34TH
INTERNATIONAL CONFERENCE

AWCBR

Australasian Winter Conference
on Brain Research

2016
Programme and Abstracts

27 to 31 August 2016
Crowne Plaza, Queenstown, New Zealand
www.otago.ac.nz/awcbr

Saturday 27 August

8.30 am - 5.30 pm		Brain Research New Zealand Annual Meeting
3.00-5.15 pm		Registration, Crowne Plaza Hotel
5.30-6.00 pm		Student Meet and Greet
6.00 pm		Opening Reception, Cash Bar
7.00 pm		Opening Remarks
7.15 pm	1.1	**PLENARY LECTURE:** **Stuart Firestein, *Columbia University, United States of America*** How biology perceives chemistry: Stimulus processing in the mammalian olfactory system

1. Sensory and Motor Systems

Chair: Johanna Montgomery

8.00 pm	1.2	**Mike Paulin, *University of Otago, New Zealand*** Heterogeneity, randomness and sparseness in neural activity can be explained by a trade-off between energy and information in spiking neurons
8.15 pm	1.3	**Bryony Nayagam, *Bionics Institute, Australia*** Using multi-electrode arrays to stimulate and record from stem cell-derived sensory neurons in vitro
8.30 pm	1.4	**John Semmler, *University of Adelaide, Australia*** Age-related differences in motor cortex plasticity after priming with paired-associative stimulation
8.45 pm	1.5	**Shelly Lin, *University of Auckland, New Zealand*** Prolonged stimulation of purinergic P2 receptors enhances neomycin-induced sensory hair cell loss in cochlear explants
9.00 pm	1.6	**Yiwen Zheng, *University of Otago, New Zealand*** Long-term brain metabolic changes in rats following tinnitus-inducing acoustic trauma: A pilot study
9.30 pm		Rugby: All Blacks vs Australia in bar Refreshments served

Sunday 28 August
Morning Session

8.00-8.30 am — Light Breakfast Available

8.30 am — 2.1 — **PLENARY LECTURE:**
Katalin Toth, *Universite Laval, Canada*

Information processing and calcium dynamics at hippocampal mossy fibre terminals

2. Neural Excitability

Chair: Tracy Melzer

9.15 am	2.2	**Johanna Montgomery, *University of Auckland, New Zealand*** Shank3 is a key component of a zinc-sensitive signaling system regulating synaptic strength that is impaired in Autism Spectrum Disorders
9.30 am	2.3	**Madeleine Kyrke-Smith, *University of Otago, New Zealand*** Inhibition of histone deacetylase activity, after LTP induction, does not promote the persistence of LTP *in vivo*
9.45 am	2.4	**Karl Iremonger, *University of Otago, New Zealand*** Corticosteriod induced functional and structural plasticity of hypothalamic corticotropin-releasing hormone (CRH) neurons
10.00 am	2.5	**Michelle Watts, *University of Queensland, Australia*** Hypoxia-regulated microRNA-210 in neuronal plasticity
10.15 am	2.6	**Steve Seo, *University of Otago, New Zealand*** Marked differences in the number and type of synapses innervating the primary dendrites of nigral versus ventral tegmental dopaminergic neurons, and nigral dopaminergic versus striatal spiny projection neurons, in the rat
10.30 am	2.7	**Steve Kerr, *University of Otago, New Zealand*** Electrophysiological assessment of silver nanoparticle toxicity in an in vitro rat hippocampal slice preparation

Sunday 28 August
Afternoon Session

3.30 pm Afternoon Tea Available

3. Disorders of the Nervous System (I)

Chair: Ping Liu

4.00 pm	3.1	**Stephen Back,** ***Oregon Health and Science University, United States of America*** Mechanisms of aberrant regeneration and repair of human cerebral white matter injury related to Vascular Cognitive Impairment and Dementia (VCID)
4.30 pm	3.2	**Andrea Kwakowsky,** ***University of Auckland, New Zealand*** Impaired $GABA_A$ receptor function in the human Alzheimer's disease hippocampus, subiculum, entorhinal cortex and superior temporal gyrus
4.45 pm	3.3	**Alisa McGregor,** ***University of Otago, New Zealand*** Varenicline produces long-lasting improvements in motor function and modulates neuroinflammation in YAC128 mice
5.00 pm	3.4	**Yu Jing,** ***University of Otago, New Zealand*** Effects of maternal immune activation on brain arginine metabolism of juvenile rat offspring
5.15 pm	3.5	**Toni Pitcher,** ***New Zealand Brain Research Institute, New Zealand*** Ethnic and regional differences in Parkinson's disease in New Zealand
5.30 pm	3.6	**Michael Babcock,** ***Montana State University, United States of America*** Deletion of CNS Ikbkap/Elp1: Murine model of Familial Dysautonomia

Conference Dinner

7.30 pm

Skyline Restaurant

Tickets must be purchased in advance.
The ticket includes return gondala transport to the restaurant.

The Skyline is a licensed restaurant but wine and beer will be provided.
The function room will be open from 7.00 pm,
with dinner commencing at 7.30 pm

Musical entertainment will be provided.

Monday 29 August
Morning Session

8.30-9.00 am Light Breakfast Available

9.00 am 4. **PLENARY LECTURE:**

Akiva Cohen, ***University of Pennsylvania, United States of America***

Excitatory/inhibitory synaptic imbalance and dietary therapy following traumatic brain injury

Chair: Cliff Abraham

5. POSTER SESSION

9.45 am - 4.30 pm

Presenters will be in attendance during this time

Presenters for Posters A will be in attendance from 9.45 to 11.15 pm

Presenters for Posters B will be in attendance from 3.00 to 4.30 pm

The poster session will be followed by a postgraduate dinner to the held at Smith's Craft Beer House from 7.00 pm to 9.00 pm

5.1 - A	**Mohamed Ibrahim,** ***University of Otago, New Zealand***
	Doxycycline mediated gene repression of mutant ataxin-1 during early postnatal development minimises the progression of mouse spino-cerebellar ataxia type 1
5.2 - B	**Haiyang Jin,** ***University of Auckland, New Zealand***
	Can brief exposure time (Under 170ms) of faces evoke N170?
5.3 - A	**Allanah Kenny,** ***University of Canterbury, New Zealand***
	Massively parallel simulations of neurovascular coupling with nitric oxide pathway and extracellular diffusion
5.4 - B	**Michaela Pettie,** ***Victoria University of Wellington, New Zealand***
	Continuous exposure to valproate during prenatal development as an animal model for autism spectrum disorder
5.5 - A	**Mohammed Rizwan,** ***University of Otago, New Zealand***
	Temporal and regional onset of leptin resistance in diet induced obese mice
5.6 - B	**Molly Swanson,** ***University of Auckland, New Zealand***
	Moderate exercise does not alter the neurogenic niches in sheep
5.7 - A	**Beatriz Calvo-Flores,** ***University of Auckland, New Zealand***
	Changes in alpha5 subunit containing GABA A receptors in the human Alzheimer's disease hippocampus

Poster Session

5.8 - B	**Jason Foote, *Victoria University of Wellington, New Zealand***
	5-HT antagonists fail to alter MDMA self-administration in rats
5.9 - A	**Nicola Mckay, *University of Auckland, New Zealand***
	Atypical matter pathways in BDNF mutation carriers
5.10 - B	**Nathan Skinner, *University of Otago, New Zealand***
	Effect of circadian rhythms on leptin sensitivity
5.11 - A	**Karan Govindpani, *University of Auckland, New Zealand***
	Cerebrovascular expression of GABA signalling components in the medial temporal gyrus of healthy and Alzheimer's disease brains
5.12 - B	**Stephanie Mercer, *University of Otago, New Zealand***
	In vivo tolerability and effects of autophagy enhancers as potential therapeutic interventions for Alzheimer's disease
5.13 - A	**Bruce Russell, *University of Otago, New Zealand***
	Greater activity in the salience network of people with schizophrenia who respond to first-line antipsychotics
5.14 - B	**Jennifer Hamilton, *University of Canterbury, New Zealand***
	Single and combined lesions of different limbic thalamic nuclei: influence on random foraging in the radial arm maze
5.15 - A	**Katie Fowler, *Victoria University of Wellington, New Zealand***
	Cognitive language difficulties in a tumour population: Three month follow-up
5.16 - B	**Ross van de Wetering, *Victoria University of Wellington, New Zealand***
	Pre-exposure to MDMA facilitates the acquisition of MDMA self-administration: Role of dopamine D2 receptors
5.17 - A	**Thulani Palpagama, *University of Auckland, New Zealand***
	Investigation of GABA signalling in an in-vivo Alzheimer's disease mouse model
5.18 - B	**Nicole Taylor, *University of Auckland, New Zealand***
	Habitual physical activity levels, the P300 and the significance of alpha power

5.19 - A **Maximilian Joret, *University of Auckland, New Zealand***

Pericyte immunosuppression in glioblastoma multiforme

5.20 - B **Jin Ng, *University of Auckland, New Zealand***

Development of in vitro models to measure the effects of plant metabolites on neuronal mitochondrial function

5.21 - A **Ashik Banstola, *University of Otago, New Zealand***

Dynamic hippocampal, orbitofrontal and subthalamic oscillations in rats performing a stop signal task

5.22 - B **Jiaxian Zhang, *University of Otago, New Zealand***

Maternal immune activation alters immunoreactive profiles of nNOS-containing neurons and microglia in postnatal day 2 rat brains

5.23 - A **Dion Henare, *University of Auckland, New Zealand***

Individual working memory performance is predicted by a neural index of distractor disengagement

5.24 - B **Dorothy Oorschot, *University of Otago, New Zealand***

Absolute number of parvicellular and magnocellular neurons in the red nucleus of the rat midbrain: A stereological study

5.25 - A **Melissa Johnston, *University of Otago, New Zealand***

A comparison of the characteristics of delay neurons in the entopallium and nidopallium caudolaterale of pigeons (Columba livia)

5.26 - B **Oliver Saltmarsh, *University of Auckland, New Zealand***

Exploring the temporal development of sensory suppression using the N170

5.27 - A **Sam Dodd, *University of Auckland, New Zealand***

Age- and gender-specific changes of the GABAA receptor signaling components in the human entorhinal cortex

5.28 - B **Mandana Ghodratipour, *University of Auckland, New Zealand***

Lipidome changes in the human caudate nucleus in Huntington's disease

5.29 - A **Madeline Nicholson, *Bionics Institute, Australia***

Differentiation, innervation and physiology of pluripotent stem cell-derived auditory neurons in vitro

5.30 - B **Yukti Vyas, *University of Auckland, New Zealand***

Zinc and NMDAR dependent changes in excitatory glutamatergic synapses expressing autism spectrum disorder associated Shank2 mutations

5.31 - A **Katharina Russell, *Lincoln University, New Zealand***

In vivo monitoring of viral mediated gene injection therapy in ovine Batten disease

5.32 - B **Tomoko Hyakumura, *Bionics Institute, Australia***

Quantification of new synapses by stem cell-derived neurons on developing peripheral and central auditory tissues in vitro

5.33 - A **Kelly Paton, *Victoria University of Wellington, New Zealand***

Analgesic and anti-inflammatory effects of novel kappa opioid receptor agonists

5.34 - B **Aline Loehfelm, *Saarland University, Germany***

Rapid effects of neurosteroids DHEA, 7α-OH-DHEA and 7β-OH-DHEA on the ACh-induced calcium-influx in honeybee (Apis mellifera) kenyon cells

5.35 - A **Sophie Barnett, *University of Canterbury, New Zealand***

Electrophysiological coherence across anterior thalamic, hippocampal and prefrontal cortex during anaesthesia after mammillothalamic tract lesions

5.36 - B **Giana Patel, *University of Auckland, New Zealand***

Competition for representation between everyday object categories as a tool to explore the functional architecture of the visual system

5.37 - A **Kaj Kamstra, *University of Otago, New Zealand***

The role of saturated and unsaturated fatty acids in neuro-inflammation and insulin sensitivity in a hypothalamic cell culture system

5.38 - B **Carolyn Wilshire, *Victoria University of Wellington, New Zealand***

An evaluation of language in brain tumour patients using a new cognitively-motivated testing protocol

5.39 - A **Michelle Goodman, *University of Canterbury, New Zealand***

Calcium dynamics in coupled cellular reaction diffusion equations

5.40 - B

Matt Oxner, *University of Auckland, New Zealand*

Breaking of Kanizsa figure completion evokes a behavior-free signal of perceptual prediction error

5.41 - A

Madhavi Pandya, *University of Auckland, New Zealand*

Age- and gender-specific changes of the GABAA receptor signalling components in the human inferior-, middle- and superior temporal gyrus

5.42 - B

Samantha Ross, *University of Otago, New Zealand*

Post-weight loss changes in brain activity after a very low calorie diet

5.43 - A

Vincent Chow, *National University of Singapore, Singapore*

A clinically authentic murine model of acute brainstem encephalitis and neurogenic pulmonary edema induced by Enterovirus 71

5.44 - B

Jessica Langbridge, *University of Canterbury, New Zealand*

A neurophysiological and behavioural assessment of interventions targeting attention bias and self-control in binge drinking

5.45 - A

Victoria Lee, *Victoria University of Wellington, New Zealand*

A “core skills” approach to the assessment of acquired language disorders

5.46 - B

Brittney Black, *University of Auckland, New Zealand*

Receptor studies suggest two neurochemically distinct populations of neurons in the human globus allidus

5.47 - A

Takanobu Yamamoto, *Tezukayama University, Japan*

The relationship between behavioral characteristics and urinary excretion of monoamine neurotransmitters in children with inattention, hyperactivity-impulsivity and ASD

5.48 - B

Fraser Doake, *University of Canterbury, New Zealand*

Epigenetic markers in the extended hippocampal memory system after diencephalic lesions

5.49 - A

Onome Okpe, *University of Otago, New Zealand*

Treatment of brain injury due to extreme prematurity: Effect of melatonin on ADHD-like hyperactivity

5.50 - B

Jarol Chen, *Lincoln University, New Zealand*

Characterisation of oxidative stress-responsive genes and gene products in ovine CLN6

Poster Session

5.51 - A	**Benjamin Aghoghovwia, *University of Otago, New Zealand***
	Effect of delayed post-treatment with adult-sourced adipose-derived mesenchymal stem cells on motor function and striatal medium-spiny projection neurons after neonatal rat hypoxia-ischemia
5.52 - B	**Rachael Sumner, *University of Auckland, New Zealand***
	Using EEG to investigate the effect of GABAergic inhibition on high frequency oscillations in the visual cortex
5.53 - A	**Emmet Power, *University of Otago, New Zealand***
	Regional changes in mouse motor cortex excitability after focal stroke
5.54 - B	**Blake Porter, University of Otago, New Zealand**
	Hippocampal place cell representations of effortful space
5.55 - A	**Helen Murray, *University of Auckland, New Zealand***
	Phenotypic characterisation of PSA-NCAM^{+} cells in the adult human brain
5.56 - B	**Shakila Rizwan, *University of Otago, New Zealand***
	Olfactory-targeted microparticles: A novel approach to bypass the blood-brain barrier
3.00 PM	Afternoon Tea Available
4.30 pm	Posters to be removed at this time
4.30 pm	Afternoon session

Monday 29 August
Afternoon Session

6. Cognition and Behaviour (I)

Chair: Karen Waldie

4.30 pm	6.1	**Kyla-Louise Horne, *University of Canterbury, New Zealand*** Risk of dementia in Parkinson's disease: Towards optimal short cognitive testing
4.45 pm	6.2	**Jessica Millar, *University of Otago, New Zealand*** Maternal immune activation alters sensitivity to action-outcome contingency in adult rat offspring
5.00 pm	6.3	**Brook Perry, *University of Canterbury, New Zealand*** Mammillothalamic tract lesions decrease theta coherence between the anterior ventral nucleus and both prefrontal cortex and hippocampus in a spatial memory task
7.00 pm		AWCBR Student Dinner Venue: Smith's Craft Beer House, 1st floor, 53 Shotover Street, Queenstown

Monday 29 August
Evening Session

7. Integrative Systems and Development

Chair: Karl Iremonger

5.15 pm	7.1	**Juliette Cheyne,** ***Netherlands Institute for Neuroscience, The Netherlands*** The fine-scale structure of spontaneous synaptic activity in the developing mouse visual cortex
5.30 pm	7.2	**Alexander Tups,** ***University of Otago, New Zealand*** Leptin resistance: Cause or consequence of hypothalamic inflammation?
5.45 pm	7.3	**Megan Barclay,** ***University of Auckland, New Zealand*** Localization of glutamatergic synapses around the sensory receptors in the mammalian inner ear during development
6.00 pm	7.4	**Alisa Boucsein,** ***University of Otago, New Zealand*** Temporal rhythms of metabolic pathways in the hypothalamus

Tuesday 30 August
Morning Session

8.00-8.30 am — Light Breakfast Available

8.30 am — 8.1

PLENARY LECTURE:
Simon Schultz, *Imperial College, United Kingdom*

Analysis of information encoding and dynamics in optically recorded cortical circuits

8. Novel Methods and Technology Development

Chair: Ruth Empson

9.15 am — 8.2

Calvin Young, *University of Otago, New Zealand*

Integrating reliable, cost-effective, open-source hardware for high throughput neurophysiological, optogenetic and behavioural experimentation in rodents

9.30 am — 8.3

Tim van Ginkel, *University of Canterbury, New Zealand*

Detailed modelling of neuronal calcium dynamics to enable validation of the NVU

9.45 am — 8.3

Meg Spriggs, *University of Auckland, New Zealand*

Network plasticity in the sensory cortices

10.00 am — 8.4

Jennifer Robertson, *Australian National University, Australia*

Unsupervised classification of excitatory neurons in layer 3 of the piriform cortex using morphological, electrical and synaptic properties

10.15 am — Tea/Coffee break

10.30 am — **ANNUAL GENERAL MEETING**
All conference participants are invited to attend

Tea/Coffee will be available for AGM attendees

Tuesday 30 August
Afternoon Session

3.30 pm — Afternoon Tea Available

9. Cognition and Behavour (II)

Chair: John Dalrymple-Alford

4.00 pm	9.1	**David Moreau,** ***University of Auckland, New Zealand*** High-intensity training enhances executive function in children
4.15 pm	9.2	**Jingwen Mao,** ***University of Auckland, New Zealand*** When do we perceive subtle facial expressions?
4.30 pm	9.3	**Susan Welsh,** ***Victoria University of Wellington, New Zealand*** The effects of kappa opioid agonists on the novel object recognition task
4.45 pm	9.4	**Shabah Shadli,** ***University of Otago, New Zealand*** Source localization of stop- and conflict-related rhythmicity

Tuesday 30 August
Evening Session

10. Disorders of the Nervous System (II)

Chair: Shakila Rizwan

5.00 pm	10.1	**Leonardo Belluscio,** ***National Institutes of Health, United States America*** APP overexpression causes Aβ-independentneuronal death through intrinsic apoptosis pathway
5.30 pm	10.2	**Ping Liu,** ***University of Otago, New Zealand*** Brain arginine metabolism is altered in patients with schizophrenia
5.45 pm	10.3	**Tessa Fuhrer,** ***University of Auckland, New Zealand*** Impaired expression of GABA transporters in the human Alzheimer's disease hippocampus, subiculum, entorhinal cortex and superior temporal gyrus
6.00 pm	10.4	**Daniel Myall,** ***New Zealand Brain Research Institute, New Zealand*** Epidemiology of Parkinson's in New Zealand: Sex, age, and future burden
6.15 pm	10.5	**Thomas Park,** ***University of Auckland, New Zealand*** Aberrant pericyte signaling in Huntington disease

Wednesday 31 August
Morning Session

8.30-9.00 am		Light Breakfast Available
9.00 am	11.1	**PLENARY LECTURE:** **Ben Harrison, *University of Melbourne, Australia***
9.45 am		Tea/Coffee break

11. Neuroimaging Symposium

Chair: Donna Rose Addis

10.00 am	11.2	**Michael Corballis, *University of Auckland, New Zealand*** Language, gesture, and handedness: Independent lateralized networks
10.15 am	11.3	**Tracy Melzer, *New Zealand Brain Research Institute, New Zealand*** Amyloid imaging and cognition in Parkinson's disease: Interim report
10.30 am	11.4	**Eileen Luders, *University of California Los Angeles, United States of America*** The corpus callosum in the human brain: Measurements and findings
10.45 am	11.5	**Reece Roberts, *University of Auckland, New Zealand*** The Simpson's paradox and fMRI: What we talk about when we talk about functional connectivity
11.00 am	11.6	**Sheena Sharma, *Auckland University of Technology, New Zealand*** White matter changes after joint replacement in people with knee osteoarthritis
11.15 am	11.7	**Catherine Morgan, *University of Auckland, New Zealand*** Clinical translation of Chemical Exchange Saturation Transfer (CEST) MRI for imaging glucose
11.45 am		Closing Remarks Light lunch and Student Prize Presentation

Email Addresses

Cliff Abraham
cabraham@psy.otago.ac.nz
Donna Rose Addis
d.addis@auckland.ac.nz
Benjamin Aghoghovwia
aghbe756@student.otago.ac.nz
Catrona Anderson
catrona.anderson@hotmail.com
Tiger Aspell
tigeraspell@hotmail.com

Michael Babcock
mbabcock@montana.edu
Stephen Back
backs@ohsu.edu
Ashleigh Baker
ashleigh.baker@auckland.ac.nz
Ashik Banstola
banas477@student.otago.ac.nz
Meagan Barclay
m.barclay@auckland.ac.nz
Sophie Barnett
sophie.barnett@pg.canterbury.ac.nz
Brittney Black
brittney.black@auckland.ac.nz
Alisa Boucsein
alisa.boucsein@postgrad.otago.ac.nz

Beatriz Calvo-Flores Guzman
bcfguzman@gmail.com
Jarol Chen
jarol.chen@lincolnuni.ac.nz
Juliette Cheyne
juliette.cheyne@gmail.com
Vincent Chow
micctk@nus.edu.sg
Gavin Clark
gavin.clark@otago.ac.nz
Akiva Cohen
cohena@email.chop.edu
Michael Corballis
m.corballis@auckland.ac.nz
Maurice Curtis
m.curtis@auckland.ac.nz

Tim David
tim.david@canterbury.ac.nz
Justin Dean
j.dean@auckland.ac.nz
Athena Dennis
a.dennis@auckland.ac.nz
Fraser Doake
fraserdoake@hotmail.com
Sam Dodd
s.dodd@auckland.ac.nz

Ruth Empson
ruth.empson@otago.ac.nz

Richard Faull
rlm.faull@auckland.ac.nz
Francesca Favero
f.favero@auckland.ac.nz
Valery Feigin
valery.feigin@aut.ac.nz
Stuart Firestein
sjf24@columbia.edu
Jason Foote
jasonkfoote@gmail.com
Katie Fowler
kt_fowler@hotmail.com
Tessa Fuhrer
t.fuhrer@auckland.ac.nz

Beau Gamble
bgam941@aucklanduni.ac.nz
Mandana Ghodratipour
m.ghodratipour@auckland.ac.nz
Andy Gibson
andy.gibson@pg.canterbury.ac.nz
Michelle Goodman
michelle.goodman@pg.canterbury.ac.nz
Karan Govindpani
k.govindpani@auckland.ac.nz

Jennifer Hamilton
jenny.hamilton@pg.canterbury.ac.nz
Ben Harrison
habj@unimelb.edu.au
Dion Henare
dion.henare@auckland.ac.nz

Email Addresses

Kyla-Louise Horne
kyla.horne@nzbri.org
Tomoko Hyakumura
thyakumura@bionicsinstitute.org

Mohamed Fasil Ibrahim
ibrmo047@student.otago.ac.nz
Karl Iremonger
karl.iremonger@otago.ac.nz

Haiyang Jin
haiyang.jin@auckland.ac.nz
Rena Jing
rena.jing@otago.ac.nz
Melissa Johnston
milliej.johnston@gmail.com
Maximilian Joret
mjor024@aucklanduni.ac.nz

Kaj Kamstra
kamka518@student.otago.ac.nz
Allanah Kenny
allanah.kenny@pg.canterbury.ac.nz
Steve Kerr
steve.kerr@otago.ac.nz
Andrea Kwakowsky
a.kwakowsky@auckland.ac.nz
Madeleine Kyrke-Smith
kyrma9307@student.otago.ac.nz

Jessica Langbridge
jesslangbridge@gmail.com
Victoria Lee
victoria_lee@hotmail.co.nz
Shelly Lin
shelly.lin@auckland.ac.nz
Ping Liu
ping.liu@otago.ac.nz
Aline Loehfelm
a.loehfelm@gmx.de
Eileen Luders
eileen.luleders@gmx.de

Ailsa McGregor
ailsa.mcgregor@otago.ac.nz
Nicole Mckay
nicole.mckay@auckland.ac.nz

Neil McNaughton
nmcn@psy.otago.ac.nz
Jingwen Mao
jmao353@aucklanduni.ac.nz
Tracy Melzer
tracy.melzer@otago.ac.nz
Stephanie Mercer
merst955@student.otago.ac.nz
Jessica Millar
jessicagrace.millar@gmail.com
Johanna Montgomery
jm.montgomery@auckland.ac.nz
David Moreau
d.moreau@auckland.ac.nz
Catherine Morgan
c.morgan@auckland.ac.nz
Helen Murray
h.murray@auckland.ac.nz
Daniel Myall
daniel.myall@nzbri.org

Bryony Nayagam
b.nayagam@unimelb.edu.au
Jin Yang Ng
jng061@aucklanduni.ac.nz
Madeline Nicholson
mnicholson@bionicsinstitute.org

Onome Okpe
okpon755@student.otago.ac.nz
Dorothy Oorschot
dorothy.oorschot@otago.ac.nz
Matt Oxner
moxn128@aucklanduni.ac.nz

Thulani Palpagama
t.palpagama@auckland.ac.nz
Madhavi Pandya
mpan968@aucklanduni.ac.nz
Thomas Park
thomas.park@auckland.ac.nz
Giana Patel
gpat480@aucklanduni.ac.nz
Kelly Paton
kelly.paton@vuw.ac.nz
Mike Paulin
mike.paulin@otago.ac.nz

Email Addresses

Brook Perry
brook.perry@pg.canterbury.ac.nz
Michaela Pettie
michaelapettie@gmail.com
Toni Pitcher
toni.pitcher@otago.ac.nz
Blake Porter
porbl004@student.otago.ac.nz
Emmet Power
emmet.power@otago.ac.nz

Mohammed Rizwan
mohammed.rizwan@otago.ac.nz
Shakila Rizwan
shakila.rizwan@otago.ac.nz
Reece Roberts
r.roberts@auckland.ac.nz
Jennifer Robertson
u4517241@anu.edu.au
Dean Robinson
d.robinson@auckland.ac.nz
Samantha Ross
samantha.ross@otago.ac.nz
Ted Ruffman
tedr@psy.otago.ac.nz
Bruce Russell
bruce.russell@otago.ac.nz
Katharina Russell
katharina.russell@lincolnuni.ac.nz

Oliver Saltmarsh
osal253@aucklanduni.ac.nz
Simon Schultz
s.schultz@imperial.ac.uk
John Semmler
john.semmler@adelaide.edu.au
Steve Seo
steve.seo@anatomy.otago.ac.nz
Shabah Shadli
shabah.shadli@otago.ac.nz
Sheena Sharma
sheena.sharma@aut.ac.nz
Nathan Skinner
skina239@student.otago.ac.nz
Meg Spriggs
mspr827@aucklanduni.ac.nz

Rachael Sumner
r.sumner@auckland.ac.nz
Molly Swanson
m.swanson@auckland.ac.nz

Nicole Taylor
ntay478@aucklanduni.ac.nz
Lynette Tippett
l.tippett@auckland.ac.nz
Katalin Toth
katalin.toth@fmed.ulaval.ca
Alexander Tups
alexander.tups@otago.ac.nz

Ross van de Wetering
ross.vandewetering@vuw.ac.nz
Tim van Ginkel
tim.vanginkel@pg.canterbury.ac.nz
Yukti Vyas
yukti.vyas@auckland.ac.nz

Karen Waldie
k.waldie@auckland.ac.nz
Michelle Watts
m.watts1@uq.edu.au
Susan Welsh
susan@welsh.co.nz
Kristina Wiebels
kwie508@aucklanduni.ac.nz
Carolyn Wilshire
carolyn.wilshire@vuw.ac.nz
Kaitlin Wolfe
wolka282@studentl.otago.ac.nz

Takanobu Yamamoto
yamamoto@tezukayama-u.ac.jp
Calvin Young
calvin.young@otago.ac.nz
Deborah Young
ds.young@auckland.ac.nz

Jiaxian Zhang
zhaje795@student.otago.ac.nz
Yiwen Zheng
yiwen.zheng@otago.ac.nz

Prize Winners

Goddard Prize and Poster Prize Winners

1990	**Steven Morrison,** University of Otago, New Zealand
1991	**Oliver Davidson,** University of Otago, New Zealand
1992	**Nadia Solowij,** University of New South Wales, Australia
1993	**Kjesten Wiig,** University of Otago, New Zealand
1994	**Niki Butterworth,** University of Auckland, New Zealand
1995	**Gerald Ahern,** John Curtin School of Medical Research, Australia
1996	**Judy Swanson,** University of Otago, New Zealand
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Abstracts

1.1

How biology perceives chemistry: Stimulus processing in the mammalian olfactory system

S. FIRESTEIN

Department of Biological Sciences, Columbia University, New York, United States of America

The mammalian nose is arguably the best chemical detector on the planet, able to detect and discriminate a large number and diverse array of molecules. This is accomplished in part by a large number of receptors (encoded by more than a thousand different genes in many species) and a very shallow central circuit, comprising only 2 synapses from the outside world to the primary olfactory cortex. While the discovery of the large family of receptors seemed to provide a molecular basis for understanding olfaction, this aspiration has required some revision due to recent findings in both the periphery and the CNS. In the periphery we must take into account antagonistic effects of many odors and a new classification of odors according to medicinal chemical principles versus pure organic chemistry. In the brain we see a cortex that does not have a clear representational molecular map and may be shaped more by output than input, in contrast with other sensory cortices. In sum, it appears that a paradigm shift is afoot in the nose.

1.2

Heterogeneity, randomness and sparseness in neural activity can be explained by a trade-off between energy and information in spiking neurons

M. G. PAULIN[1], K. F. PULLAR[1], and L. F. HOFFMAN[2]

[1]*Department of Zoology, University of Otago, Dunedin, New Zealand*

[2]*David Geffen School of Medicine, University of California Los Angeles, Los Angeles, United States of America*

Spiking neurons are energetically expensive, mainly because of the cost of spiking. Yet the vestibular system employs thousands of them to tell the brain about each degree of freedom of movement. These neurons respond to head movements with diverse, highly variable spiking activity. How could such a large, noisy population of neurons be efficient? We recorded activity from semicircular canal afferent neurons in chinchillas. Computationally intensive statistical analysis showed that despite the superficial diversity of afferent spiking patterns, inter-spike intervals for each neuron are samples from a generalized inverse Gaussian (GIG) probability density. We later discovered that GIG interspike interval densities maximize the efficiency of spiking channels measured in bits per second per nanowatt. Combining the information transmitted by all of its noisy neurons shows that the vestibular nerve overall is an efficient channel for rapid transmission of precise, high-bandwidth signals, with effectively no noise. This paradoxical result can be explained by a simple model in which stochastic post-spike inhibition in a neuron causes a loss of information, but saves enough energy to pay for that information to be transmitted by other neurons in the population. Heterogeneity, randomness and sparseness are generic features of spiking activity in nervous systems, including in mammalian cortex, which may be explained by this principle.

1.3

Using multi-electrode arrays to stimulate and record from stem cell-derived sensory neurons *in vitro*

B. A. NAYAGAM[1,2], A. ALSHAWAF[3], W. QIU[3], S. SKAFIDAS[3], and M. DOTTORI[3]
[1]Bionics Institute, Melbourne, Australia
[2]Department of Audiology and Speech Pathology, [3]Centre for Neural Engineering, University of Melbourne, Melbourne, Australia

Stem cell-derived (SCD) sensory neurons may provide a source of replacement cells for individuals with severe deafness, where few neurons remain. In such cases, SCD sensory neurons would require appropriate depolarisation from a cochlear implant in order to precisely relay sound information to the brain. Electrical stimulation (ES) of the auditory nerve causes significantly higher firing rates in auditory neurons. Thus, we have investigated the firing properties of SCD sensory neurons using multi-electrode arrays (MEAs), including the ability of these neurons to form functional networks. We utilised our published protocols to derive functional sensory neurons from human pluripotent stem cells. SCD sensory neurons were cultured on MEAs for up to 6 weeks *in vitro* and exposed to 2 Hz biphasic voltage pulses (±800 mV, 200 µsec per phase) for 5 minutes, twice a week. Following experimentation, cultures were immunostained for a cohort of neurosensory markers. SCD sensory neurons expressed numerous sensory- and neural-specific markers, were spontaneously active after 9 days differentiation, and generated action potentials in response to membrane depolarisation after 14 days differentation. *In vitro* ES of SCD sensory neurons using MEAs produced maximum array wide spike rates of 195.8 ± 110.3 spikes/sec and spontaneous firing activity developed into trains of spikes and bursting, reaching a maximum number of 1021.3 ± 626.1 bursts. The electrical activity and network forming capacity of SCD sensory neurons can be measured and quantified using MEA *in vitro*. Current experimentation includes comparing a number of different ES regimes for enhancing firing activities in these cell populations.

1.4

Age-related differences in motor cortex plasticity after priming with paired-associative stimulation

J. G. SEMMLER[1], A POST[1,2], G. M. OPIE[1], M. C. RIDDING[1], and U. ZIEMANN[3]
[1]School of Medicine, University of Adelaide, Adelaide, Australia
[2]Center for Human Movement Science, University of Groningen, Groningen, Netherlands
[3]Department of Neurology, Eberhard Karls University of Tübingen, Tübingen, Germany

Previous studies in young subjects show that priming with paired associative stimulation (PAS) can alter the plastic response to a subsequent PAS protocol, with divergent effects in primary motor cortex (M1) following priming with long-term potentiation (LTP) and depression (LTD)-like protocols. The aim of this study was to compare priming effects with PAS on M1 plasticity in young and older adults. Fifteen young (20-27 yrs) and fourteen old (61-79 yrs) subjects participated in 3 experimental sessions, with each session involving two consecutive PAS protocols separated by 10 mins. PAS consisted of 200 pairs of right ulnar nerve stimulation followed by transcranial magnetic stimulation of the left M1. The first (priming) protocol was either PAS LTP (ISI=N20 latency+2 ms), PAS LTD (ISI=N20 latency-10 ms), or PAS Control (ISI=100 ms), whereas the second (test) protocol was always PAS LTP. Changes in M1 excitability were assessed from motor evoked potentials (MEPs) in a hand muscle. In young subjects, MEPs were larger after LTP-LTP compared with LTD-LTP ($P<0.0001$) or Control-LTP ($P=0.0003$), whereas MEPs were larger after Control-LTP compared with LTD-LTP ($P<0.0001$). In old subjects, MEPs were smaller after LTP-LTP compared with LTD-LTP ($P=0.0003$) and Control-LTP ($P=0.01$), but there was no difference between LTD-LTP and Control-LTP ($P=0.8$). In addition, MEPs were greater in young compared with old subjects following both LTP-LTP ($P=0.001$) and sham-LTP ($P=0.04$). Data show that priming with PAS LTP is most effective in young subjects, but priming with PAS LTP or LTD did not enhance M1 plasticity in older adults.

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1.5

Prolonged stimulation of purinergic P2 receptors enhances neomycin-induced sensory hair cell loss in cochlear explants

S. C. Y. LIN[1], P. R. THORNE[1,2], and S. M. VLAJKOVIC[1]
[1]Department of Physiology and Centre for Brain Research, [2]Section of Audiology, University of Auckland, Auckland, New Zealand

Neomycin, an aminoglycoside used for the treatment of tuberculosis and other serious gram negative bacterial infections, has considerable ototoxic side effects, causing the loss of sensory hair cells in the cochlea. ATP signalling in the cochlea activates ionotropic P2X and metabotropic P2Yreceptors, thus increasing intracellular calcium concentrations in hair cells. We hypothesise that prolonged stimulation of P2X receptors can increase the pore size of the ion channel, which can lead to increased neomycin uptake and accelerated apoptosis. We have previously demonstrated an increased susceptibility of the basal turn hair cells to ototoxic effects of neomycin after incubation with ATPγS, a slowly hydrolysable analogue of ATP and $P2X_2$ receptor agonist. This study investigated calcium transients and neomycin uptake in cochlear explants incubated with ATPγS. Organ of Corti explants from C57BL/6 mice (postnatal day 3) were incubated for 3 hours in normal culture medium containing neomycin Texas-red conjugate (NTR) with or without ATPγS. No significant differences were identified in NTR uptake between the control explants incubated in normal culture medium and explants supplemented with ATPγS. However, Fura-2 340/380nm ratiometric fluorescence used to measure changes in intracellular calcium concentration detected a significantly stronger ATPγS-induced fluorescence in hair cells pre-incubated with neomycin (neo: 0.049 ± 0.015, control: 0.016 ± 0.005, $p < 0.001$, Mann-Whitney test). The results suggest that ATPγS aggravates ototoxic effects of neomycin in the basal turn by increasing calcium influx through $P2X_2$ receptors rather than neomycin uptake. This study demonstrates that P2X receptors contribute to increased neomycin ototoxicity in the cochlear basal turn which can lead to high frequency hearing loss.

1.6

Long-term brain metabolic changes in rats following tinnitus-inducing acoustic trauma: A pilot study

Y. ZHENG[1,2], J. AA[3], J. HE[3], Y. ZHU[3], S. VAGAL[1,2], G. WANG[3], and P. F. SMITH[1,2]
[1]Department of Pharmacology and Toxicology, [2]Brain Health Research Centre, University of Otago, Dunedin, New Zealand
[3]Key Laboratory of Pharmacokenetics and Drug Metabolism, China Pharmaceutical University, Nanjing, China

It has been increasingly recognized that tinnitus is likely to be generated by a complex network changes involving not only the auditory system but also systems related to memory, emotion and stress. One obvious and significant gap is a lack of predictive biomarkers that reflect the consequences of this interactive 'tinnitus-causing' network. In this study, we analysed brain metabolic changes in 11 different brain regions of rats following tinnitus-inducing acoustic trauma using metabolomics. Using GC/MS, a total of 107 distinct peaks were found and 88 were identified as authentic by comparing each peak with that available in the libraries and that of the reference compound. Data were analyzed using both principal component analysis and partial least squares projection to latent structure-discriminant analysis. Although the composition of metabolites varied among different brain regions, brain regions with similar functions tend to have similar metabolite compositions. Acoustic trauma did not change the metabolite clusters in these regions. However, when analysed within each brain regions, proline, serine, N-acetyl aspartic acid and γ-aminobutyric acid showed distinct separation between control and acoustic trauma groups in the auditory cortex, inferior colliculus, superior colliculus, vestibular nucleus complex and cerebellum. Further metabolic pathway impact analysis and the enrichment overview with network analysis suggest the primary involvement of the glutamate, arginine, proline as well as the purine metabolic pathways. Our results provide the first metabolomics evidence that acoustic trauma and perhaps tinnitus induce changes in multiple metabolic pathways.

2.1

Information processing and calcium dynamics at hippocampal mossy fibre terminals

K. TOTH

Centre de Recherche, Universite Laval, Quebec, Canada

Presynaptic terminals play a key role in the translation of presynaptic firing patterns to a neurotramsitter release profile. Unique features of the presynaptic terminal will determine for example whether repeated firing leads to increased (facilitation) or decreased (depression) neurotransmsitter release. The process of signal translation is largely defined by presynaptic calcium dynamics. Neuronal calcium elevations are shaped by several key parameters, including the properties, density, and the spatial location of voltage-gated calcium channels (VGCCs). Short-term plasticity is synapse-specific, the same firing pattern is 'inetrpreted' differently by various neurons. What is the structural and functional reason of this diversity? How do the same building blocks endow terminals with synapse-specific features? We identified two distinct presynaptic mechanisms that are involved in short-term facilitation in hippocampal mossy fibers. The combination of multivesicular release and the recruitment of additional release sites act together to increase glutamate release during burst activity. This is supported by the compartmentalized spatial profile of calcium elevations in boutons and helps to expand the dynamic range of mossy fibers information transfer. We also identified the specialized roles different types of VGCCs play in neurotrmanitter release. N-type VGCCs permit fast glutamate release at a limited number of release sites and support short-term facilitation by enhancing multivesicular release through close association with active zones. In contrast, Ca^{2+} entry via P/Q-type VGCCs promotes the recruitment of additional release sites through activity-dependent homogenization of Ca^{2+} elevations. This is made possible by the strategic distribution of P/Q-type VGCCs further away from active zones. Altogether, our results highlight the specialized contribution of P/Q- and N-types VGCCs to neurotransmitter release.

2.2

Shank3 is a key component of a zinc-sensitive signaling system regulating synaptic strength that is impaired in Autism Spectrum Disorders

J. M. MONTGOMERY[1], K. LEE[1], M. ARONS[2], C. MUNRO[1], S. KIM[2], and C. C. GARNER[2,3]

[1]*Department of Physiology, University of Auckland, Auckland, New Zealand*

[2]*Department of Psychiatry and Behavioral Sciences, Stanford University, Palo Alto, United States of America*

[3]*German Center for Neurodegenerative Diseases, Charite University, Berlin, Germany*

At excitatory synapses, glutamate receptors and synaptic proteins are localised to the postsynaptic density (PSD) at the tips of dendritic spines. Proteins within the PSD are critical for receptor localisation and trafficking, as well as controlling synapse function and plasticity. Shank3 is a multidomain PSD scaffold protein also known as the "master regulator" of excitatory synapses. Functional studies *in vivo* and *in vitro* support the concept that Shank3 is critical for synaptic plasticity and the trans-synaptic coupling between the reliability of presynaptic neurotransmitter release and postsynaptic responsiveness. Yet, how Shank3 regulates synaptic strength remains unclear. The C-terminus of Shank3 contains a SAM domain that is essential for its postsynaptic localisation. It also binds zinc thus raising the possibility that changing zinc levels modulates Shank3 function in dendritic spines. In support of this hypothesis, we have found that zinc is a potent regulator of Shank3 activation and dynamics in rat hippocampal neurons. Moreover, we show that zinc modulation of synaptic transmission is Shank3 dependent. Interestingly, an Autism Spectrum Disorder (ASD)-associated variant of Shank3 ($Shank3^{R87C}$) retains its zinc sensitivity and supports zinc-dependent activation of excitatory synaptic transmission. However, elevated zinc was unable to rescue defects in trans-synaptic signaling caused by the R87C mutation, implying that trans-synaptic increases in neurotransmitter release are not necessary for the postsynaptic effects of zinc. Together these data suggest that Shank3 is a key component of a zinc-sensitive signaling system, regulating synaptic strength that may be impaired in ASD.

2.3

Inhibition of histone deacetylase activity, after LTP induction, does not promote the persistence of LTP *in vivo*

M. KYRKE-SMITH[1,2,3], W. C. ABRAHAM[2,3], and J. M. WILLIAMS[1,3]
[1]Department of Anatomy, [2]Department of Psychology, [3]Brain Health Research Centre, University of Otago, Dunedin, New Zealand

The maintenance of long-term potentiation (LTP), a mechanism underlying long-term memory, is critically dependent upon regulated gene expression. Indeed, inhibition of histone deacetylases (HDACs), which are negative regulators of gene expression, around the time of LTP induction enhances its persistence *in vitro*. Further, using an *in vivo* LTP model, we have previously reported that HDAC1 activity is increased 12 h post-LTP induction. This suggests that HDAC1 is regulated at times other than during the initial induction period. Thus, we hypothesize that HDAC1 may act to control groups of genes which stabilise LTP over the long term. To investigate this hypothesis, we tested the effect of inhibiting HDAC activity on LTP persistence at the perforant path-dentate gyrus synapses of awake, freely moving, male Sprague-Dawley rats. To determine the optimal regime for administration of the HDAC inhibitor Trichostatin A (TSA), we used immunohistochemistry to measure the increase in histone acetylation arising from inhibiting deacetylation; the maximum increase was found to occur 4 h after injection of 2 mg/kg TSA (t-test, $p<0.05$). Therefore, to target the 12 h timepoint, we compared the persistence of LTP in animals injected with TSA or vehicle, 8 h post-LTP induction (n=7 per group). Contrary to prediction, we found that TSA had no effect on the persistence of LTP over 21 days (2-way repeated measures ANOVA). These results suggest that HDAC activity 12 h post-LTP is not critical to LTP persistence over the time period investigated.

2.4

Corticosteriod induced functional and structural plasticity of hypothalamic corticotropin-releasing hormone (CRH) neurons

K. J. IREMONGER and T. BITTAR
Centre for Neuroendocrinology, Brain Health Research Centre, Department of Physiology, University of Otago, Dunedin, New Zealand

Corticotropin-releasing hormone (CRH) neurons are the final output cells of a complex neural network that controls the neuroendocrine stress response. Activation of CRH neurons ultimately leads to enhanced secretion of stress hormones from the adrenal gland. Long-term elevations in stress hormone levels can induce plasticity in neural networks, however, the effects on CRH neuron structure and function are unclear. To investigate this, mice were treated for 14 days with 25µg/ml corticosterone (CORT) in the drinking water or vehicle for control. Brain slices were then prepared and patch clamp recordings were obtained from CRH neurons to record cellular excitability and fill neurons with neurobiotin for morphological reconstructions. Patch-clamp recordings revealed that CORT treatment reduced intrinsic excitability of CRH neurons and altered action potential kinetics. Cellular reconstructions from control animals revealed that CRH neurons were multipolar with 1-3 primary dendrites (mean= 2.0 ± 0.1, n=36) and 0-3 secondary dendrites (mean 0.8 ± 0.1). The average total dendritic length was 335±24 µm with dendrites having a low density of dendritic spines (0.17±0.01 spines/µm). Axons were found to originate from the primary dendrite in 61% of neurons and the soma in 39% of neurons. Exposure to 14 days CORT did not significantly change any of these gross dendritic or axonal parameters (n=33 cells). However, CORT treated animals had a significantly lower density of dendritic spines (0.05±0.01 spines/µm). Overall, these data reveal the dendritic and axonal features of CRH neurons for the first time. In addition, these data show that exposure to elevated CORT levels reduces intrinsic excitability and dendritic spine density, however, does not lead to large-scale dendritic reorganization.

2.5

Hypoxia-regulated microRNA-210 in neuronal plasticity

M. E. WATTS[1], S. M. WILLIAMS[2], and C. CLAUDIANOS[3]
[1]Queensland Brain Institute, [2]Diamantina Institute, University of Queensland, Brisbane, Australia
[3]Monash Institute of Cognitive and Clinical Neuroscience, Monash University, Melbourne, Australia

The hypoxia-regulated microRNA-210 (miR-210) is a highly conserved miRNA, known to regulate metabolism and cell cycle under hypoxic conditions. Recently in our lab we found that miR-210 is also involved in honeybee learning and memory, raising the question of how neural activity may induce hypoxia regulated genes and in turn how miR-210 may regulate plasticity not only in insects but also in more complex mammalian systems. Using a biotin pull-down approach in the human-derived SH-SY5Y neuroblastoma cell system we have experimentally identified 1077 unique target genes of miR-210 by RNAseq. Of note among these targets there was a significant enrichment of neurodegenerative KEGG pathways including Alzheimer's, Huntington's and Parkinson's disease. Among pulled-down target genes we also identified a number of genes known to be regulated by neuronal activity and with significant neural-plasticity functions. Using dual-luciferase assays we have validated that miR-210 directly interacts and down-regulates genes including the NMDA-R subunit GRINA, the translation initiation binding protein EIF4EBP1 and the beta-actin isoform, ACTB. This was a significant finding as actin dynamics are crucial to neuronal plasticity and evidence from our lab suggests miR-210 may target the homologous, actin 5C (*Act5C*) in insects, indicating a potentially conserved regulatory pathway of miR-210. Additionally we have shown that miR-210 overexpression results in significant morphological changes in neuronal-like differentiated SH-SY5Y cells, including decreased neurite length and neurite branching. This data suggests a potentially novel mechanism of how innately occurring metabolic changes may couple plasticity to neuronal activity through hypoxia-regulated genes such as miR-210.

2.6

Marked differences in the number and type of synapses innervating the primary dendrites of nigral versus ventral tegmental dopaminergic neurons, and nigral dopaminergic versus striatal spiny projection neurons, in the rat

S. SEO, L. GODDARD, L. C. PARR-BROWNLIE, R. J. SIZEMORE, and D. E. OORSCHOT
Department of Anatomy, Brain Health Research Centre, University of Otago, Dunedin, New Zealand

Elucidating the link between cellular activity and goal-directed behavior requires a fuller understanding of the mechanisms underlying burst firing in midbrain dopaminergic neurons. Here we characterized the afferent synaptic connections onto the primary and secondary dendrites of dopaminergic neurons in the rat substantia nigra pars compacta (SNpc). We compared these data with our published results from rat dopaminergic neurons in the ventral tegmental area (VTA) and striatal cholinergic interneurons and spiny projection neurons (J. Comp. Neurol. 524:1062-1080, 2016). We found a two times greater number of symmetrical synapses per µm, and a significant increase in the percentage of symmetrical synapses, on the primary dendrites of VTA versus SNpc dopaminergic neurons. Similarly, we previously observed a two times greater absolute number of somatic synapses on VTA dopaminergic neurons compared with SNpc dopaminergic neurons. The number of synapses, and of symmetrical synapses, per µm of primary dendrite was significantly higher on striatal spiny projection neurons compared to SNpc dopaminergic neurons. No differences were evident in: (i) the number and type of synapses on the primary dendrites of dopaminergic neurons in the SNpc of Wistar versus Sprague-Dawley rats, and (ii) the number and type of synapses innervating the primary versus secondary dendrites of SNpc dopaminergic neurons. The striking anatomical differences observed could contribute to known differences in physiological responses of each neuronal subtype to afferent synaptic activity. These data are pivotal for increasing knowledge on structural/functional correlates at the level of the synaptic connectome.

2.7

Electrophysiological assessment of silver nanoparticle toxicity in an *in vitro* rat hippocampal slice preparation

D. S. KERR[1], S. PARKER[1], G. COTTON[2], C. MELEDANDRI[2], J. FALCONER[3], and D. W. GRAINGER[3]
[1]Department of Pharmacology and Toxicology, [2]Department of Chemistry, University of Otago, Dunedin, New Zealand
[3]Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, United States of America

Worldwide commercial use of silver nanoparticles (SNPs) is increasing; current applications include fabrics, contraceptives, antibiotics and disinfectants. Increasing exposures combined with evidence that SNPs cross the blood-brain barrier, warrant further toxicological characterisation of SNPs. Here, we assessed $AgNO_3$ and three different SNP preparations in a well-defined brain slice preparation. Hippocampal slices (400 µm sections) were prepared from male SD rats and maintained in a brain slice recording chamber superfused with carboxygenated ACSF (mM: 124 NaCl, 3.2 KCl, 1.25 $NaHPO_4$, 26 $NaHCO_3$, 2.0 $CaCl_2$, 2.0 $MgCl_2$, 10 glucose) at room temperature. Schaffer collateral-commissural evoked CA1 population spikes and field EPSPs were recorded with wire microelectrodes positioned in *stratum pyramidale* and *stratum radiatum*, respectively. Population spike amplitude (mV), spike area (mV.ms), and fibre spike and EPSP slopes (mV/ms) were assessed off-line. Input/output and paired pulse tests were performed before and after $NaNO_3$ (control), $AgNO_3$ and SNP administration. Both $AgNO_3$ and SNP's dramatically reduced population spikes and field EPSPs in a time-dependent fashion (from 30 min to 4 hrs). Fibre spikes were largely unaffected by silver, and paired-pulse 2nd spike amplitudes were equivalent to control conditions, suggesting that the toxic effect may be related to disruption of presynaptic release mechanisms.

3.1

Mechanisms of aberrant regeneration and repair of human cerebral white matter injury related to Vascular Cognitive Impairment and Dementia (VCID)

S. A. BACK, T. SRIVASTAVA, D. McNEAL, and D. BRANDNER
Departments of Pediatrics and Neurology, Oregon Health and Science University, Portland, United States of America

Progress to define mechanisms of diffuse white matter injury (dWMI) in aging individuals has been hampered by fundamental gaps in understanding mechanisms of remyelination failure, a central feature of VCID. We have pursued a glial progenitor-focused analysis of dWMI in human brain tissue obtained at rapid autopsy from a large population-based cohort of subjects from Seattle followed with serial cognitive testing for VCID. Remyelination failure in VCID is believed to be initiated by irreversible ischemic degeneration of myelinating oligodendrocytes (OLs). We demonstrated that VCID is accompanied by significant oxidative damage to cerebral white matter that is independent of the burden of Alzheimer's disease pathology. Oxidative damage targets both glial and axonal elements with resultant abnormal microstructure, as defined by *ex vivo* high field MRI. This damage triggers diffuse reactive astrogliosis and disrupts the extracellular matrix, which we linked to aberrant myelin repair through pathological elevations in the glycosaminoglycan hyaluronan (HA). Elevated HA was associated with a significant expansion in the OL progenitor (OPC) pool and impaired OL maturation. Using a novel in vitro slice culture model of chronic WMI and primary OPC cultures, we found that HA actions are mediated cell autonomously via specific bioactive forms of HA that block OPC maturation and myelination. A distinct size range of HA fragments promote remyelination failure via a receptor complex that involves Toll-like receptors 2 and 4 but not the classical HA receptor CD44. HA ligands activate a downstream MyD88-independent inflammatory signaling pathway that blocks OPC maturation via a tolerance-like mechanism that chronically blocks Akt-dependent pathways that normally promote myelination.

3.2

Impaired $GABA_A$ receptor function in the human Alzheimer's disease hippocampus, subiculum, entorhinal cortex and superior temporal gyrus

A. KWAKOWSKY[1], B. J. L. SYNEK[1,2], C. TURNER[1,2], H. J. WALDVOGEL[1], and R. L. M. FAULL[1]
[1]Department of Anatomy and Medical Imaging and Centre for Brain Research, University of Auckland, Auckland, New Zealand
[2]Department of Anatomical Pathology, LabPlus, Auckland City Hospital, Auckland, New Zealand

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the central nervous system. GABA type A receptors ($GABA_A$Rs) are severely affected in Alzheimer's disease (AD), an incurable and debilitating neurodegenerative disorder. However, which $GABA_A$Rs subunits exhibit most change remains controversial. In this study, we examined the expression of $GABA_A$Rs subunits (alpha1,2,3,5; beta1,2,3; gamma2) in human control and AD hippocampus (CA1-3, dentate gyrus (DG)), subiculum, entorhinal cortex and superior temporal gyrus using immunohistochemistry and confocal microscopy. In late-stage AD tissue samples we found significant alterations of all $GABA_A$Rs subunits except the beta1 that was well preserved. The most prominent changes ($P<0.001$) include an increase in $GABA_A$R alpha1 expression associated with AD in all layers of the CA3 region, in the stratum granulare and hilus of the DG. We found a significant increase in $GABA_A$R alpha2 expression in the stratum oriens of the CA1-3, stratum radiatum of the CA2,3 and decrease in the stratum pyramidale of the CA1 region in AD cases. In AD there was a significant increase in $GABA_A$R alpha5 expression in the stratum pyramidale, stratum oriens of the CA1 region and decrease in the superior temporal gyrus. We also found a significant decrease in $GABA_A$R beta3 immunoreactivity in the stratum oriens of the CA2, stratum granulare and stratum moleculare of the DG. These findings demonstrate that the expression of the $GABA_A$Rs shows severe brain region and layer specific alterations in AD and a possible co-regulation of different subunits.

3.3

Varenicline produces long-lasting improvements in motor function and modulates neuroinflammation in YAC128 mice

A. L. McGREGOR[1], G. D'SOUZA[2], and M. D. TINGLE[3]
[1]School of Pharmacy, University of Otago, Dunedin, New Zealand
[2]School of Pharmacy, [3]Department of Pharmacology and Clinical Pharmacology, University of Auckland, Auckland, New Zealand

The nicotinic agonist varenicline improves motor function and aspects of cognition in patients with early Huntington's disease (HD). Parallel studies in YAC128 transgenic mice demonstrate that functional improvements are accompanied by neuropathological changes. This study examined the persistence of motor improvements in YAC128 mice and the effect of varenicline on neuroinflammation. Thirteen month old YAC 128 mice (n=15/group) and age matched wild-type (WT) littermates (n=6/group) were administered varenicline (1mg/kg/day) for 14 days via subcutaneously implanted miniosmotic pump. Performance in the accelerating rotarod test was assessed pre and 2 weeks post pump insertion and at 2, 4, 6, 8 and 10 weeks after pump removal. Animals were killed at week 10 and a Milliplex® MAP 22-plex array used to measure cytokine concentrations in homogenates from striatum, hippocampus, cortex and cerebellum. Varenicline treatment significantly increased latency to fall in aged YAC128 mice (predrug: 26 ± 5 s vs post-drug: 47 ± 6 s, $p < 0.001$). Fall latency remained significantly increased compared to baseline performance following 8 (44 ± 6 s, $p < 0.05$) but not 10 weeks of washout (36 ± 6 s, $p = 0.895$). Varenicline treatment decreased IL-2 and IL-9 and INF-γ levels in striatum, cortex and cerebellum and 1L-1β, IL-10, IL-12, IL-15 concentrations in the cortex and cerebellum of YAC128 mice. In summary, varenicline produced long-lasting improvements in motor function in late-stage YAC128 mice, which persisted for several weeks beyond drug clearance. Reductions in pro-inflammatory cytokine concentrations remained apparent after functional benefits were lost. These results suggest varenicline has disease-modifying potential in HD.

3.4

Effects of maternal immune activation on brain arginine metabolism of juvenile rat offspring

Y. JING[1,4], H. ZHANG[2,4], D.K. BILKEY[3,4], and P. LIU[1,4]

[1]Department of Anatomy, [2]School of Pharmacy, [3]Department of Psychology, [4]Brain Health Research Centre, University of Otago, Dunedin, New Zealand

Schizophrenia is a debilitating psychiatric disorder associated with prominent prefrontal and hippocampal dysfunction, and where altered brain arginine metabolism has been implicated in the pathogenesis of the disease. Maternal immune activation (MIA) is a neurodevelopmental animal model of schizophrenia, which uses a single systemic administration of the synthetic cytokine inducer polyinosinic–polycytidilic acid during mid-gestation (GD15) to induce MIA in pregnant animals. A number of behavioral and neural features of schizophrenia are evident in the MIA offspring. The present study aimed to investigate how MIA affected brain arginine metabolism in both male and female offspring at pre-puberty age. On postnatal day 35, MIA rat offspring and their age-matched controls (n = 7/gender/group from 7 litter groups) were sacrificed. The prefrontal cortex and the CA1, CA2/3 and dentate gyrus sub-regions of the hippocampus were collected for the quantification of the tissue content of L-arginine and its downstream metabolites using liquid chromatography/mass spectrometry and high performance liquid chromatography. There were significantly increased agmatine levels in the dentate gyrus in both male and female MIA offspring, and increase putrescine level in the CA1 sub-region of the hippocampus in female MIA offspring only, with no marked differences in other metabolites. These results, for the first time, demonstrate that a single MIA insult leads to altered arginine metabolism (agmatine and putrescine in particular) in the hippocampus in the juvenile offspring. These changes may contribute to the behavioral and neural alterations seen in MIA offspring during adulthood.

3.5

Ethnic and regional differences in Parkinson's disease in New Zealand

T. L. PITCHER[1,2], D. J. MYALL[1], M. R. MACASKILL[1,2], J. F. PEARSON[3], C. LACEY[4], J. C. DALRYMPLE ALFORD[1,5,6], and T. J. ANDERSON[1,2,6,7]

[1]New Zealand Brain Research Institute, Christchurch, New Zealand

[2]Department of Medicine, [3]Biostatistics and Computational Biology Unit, [4]Department of Psychological Medicine, University of Otago, Christchurch, New Zealand

[5]Department of Psychology, University of Canterbury, Christchurch, New Zealand

[6]Brain Research New Zealand, [7]Department of Neurology, Christchurch Hospital, Christchurch, New Zealand

Information on Parkinson's-related medications was extracted from the national pharmaceutical database of community-dispensed medications for the period 1 January 2005 to 31 December 2014 for all of New Zealand. Drug-tracing methods were used to establish the likelihood of a Parkinson's diagnosis for those over 20 years of age. Calibration of estimates was completed with diagnosis confirmation for a sub-set of people, achieved through national mortality and hospital admissions databases. Prevalence and incidence rates were calculated for 2013 using Statistics New Zealand data, and were age-sex-standardized using the New Zealand 2013 population age-sex profile. Prevalence and incidence were higher in the European ethnic group compared to other ethnicities. Age-sex-standardized rates - prevalence; European: 235, Asian: 177, Pasifika: 157, and Māori: 101: per 100,000 population and incidence; European: 33, Asian: 26, Pasifika: 23, and Māori: 19 per 100,000 person-years, respectively. The potential impact of smoking and gout rates within each ethnic group were considered, but only accounted for a small proportion of the differences. There was large variation in observed rates by region, which was reduced after age-sex-ethnicity standardisation. This geographical variation suggests a need for assessment of regional resources for Parkinson's. Varying genetic and environmental factors, as well as differing healthcare access rates, are potential contributors to the observed ethnic differences.

3.6

Deletion of CNS *Ikbkap/Elp1: Murine model of Familial Dysautonomia*

M. BABCOCK and K. KUJAWA

Department of Psychology, Montana State University, Bozeman, United States of America

Familial Dysautonomia (FD) is a hereditary sensory and autonomic neuropathy (HSAN III). The laboratory of Dr F. Lefcort (Montana State University, USA) has generated mice in which *Ikbkap/Elp1* is deleted from neurons in the CNS. As a result, these mice dmelzevelop a neurodegenerative condition that is progressive and mimics many features of FD. The present study evaluated the behavioral phenotype of CNS *Ikbkap/Elp1* deletion (CKO) and age-matched (45 days) control mice. Subjects were tested in an open-field apparatus, an object recognition task, and an elevated plus maze. CKO mice tested in an open field task were significant more active (distance travelled) and spent more time in the center region of the arena compared to controls. CKO mice explored objects more, but exhibited no impairment in recognizing novelty relative to controls. In the elevated plus maze, CKO mice spent more time in the open arms compared to controls and made significantly more head dips over the edges of the open arms. These data support the conclusion that CKO mice, relative to littermate controls, have reduced anxiety. These findings are inconsistent with published reports that FD patients often exhibit a heightened anxiety state. Although speculative, we hypothesize that anxiety manifested in human FD patients may in part be in response to an awareness of their life threating medical condition and social cues. We are currently utilizing other tasks to further characterize the cognitive and emotional phenotype of this novel model of FD.

4.

Excitatory/inhibitory synaptic imbalance and dietary therapy following traumatic brain injury

A. COHEN[1,2]

[1]*Department of Anesthesiology and Critical Care Medicine Perelman School of Medicine, University of Pennsylvania, Philadelphia, United States of America*

[2]*Children's Hospital of Philadelphia, Philadelphia, United States of America*

Traumatic Brain Injury (TBI) afflicts up to 1.5 million people in the United States each year and even mild TBI can lead to a vast array of long-lasting neurological impairments including deficits in learning and memory and a reduction in seizure threshold. The hippocampus is critically involved in both of these phenomena, and highly susceptible to damage from traumatic brain injury. Optimal brain function requires a delicate balance between excitatory and inhibitory neurotransmission (E/I balance). In TBI, as in epilepsy and other CNS disorders, E/I balance is disrupted. Currently, no therapy exists to mitigate or treat the underlying causes of cognitive impairments suffered by TBI patients. To model mild TBI (mTBI) in mice, we employed lateral fluid percussion injury (LFPI). LFPI is a commonly used rodent model of brain injury that reproduces many key features of human TBI including neuronal cell loss, gliosis, ionic perturbation and memory deficits (Dixon et al., 1987, McIntosh, 1987, 1989, Smith et al., 1991). One week following LFPI we conducted various frontolimbic region-dependent memory tests and investigated electrophysiological alterations in frontolimbic activity. We report that LFPI causes hippocampal, medial prefrontal cortex (mPFC) and amydala-dependent memory impairment and regional imbalances in excitatory and inhibitory synaptic transmission. In particular, area CA1, mFPC and amygdala demonstrate a decrease in net synaptic efficacy while the dentate gyrus demonstrates an increase in net synaptic efficacy. Furthermore, our laboratory has shown that dietary supplementation with branched chain amino acids (BCAAs) leucine, isoleucine, and valine initiated 48 hours after LFPI and maintained for 5 days restores net synaptic efficacy in the mouse hippocampus and re-instates hippocampal dependent cognitive function at 7 days following LFPI.

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Poster 5.1

Doxycycline mediated gene repression of mutant ataxin-1 during early postnatal development minimises the progression of mouse spino-cerebellar ataxia type 1

M. F. IBRAHIM, E. M POWER, and R. M. EMPSON
Department of Physiology, Brain Research New Zealand, University of Otago, Dunedin, New Zealand

Spino-cerebellar ataxia type 1 (SCA1) is a human autosomal dominant movement disorder featuring an unstable expanded CAG trinucleotide (Q) repeat (39-82Q) in the ataxin-1 gene. Symptoms arise in adulthood and are accompanied by cerebellar atrophy. The aim of this study was to identify the impact of 82Q overexpression in Purkinje neuron (PN) during early cerebellar development prior to the onset of ataxic symptoms. We used a PN specific conditional Tet-OFF (doxycycline, dox, regulated) transgenic SCA1 mouse that overexpresses 82Q repeats in the ataxin-1 gene. To understand the impact of 82Q during development, we treated mice with dox 200 mg/kg in their diet for the first 6 weeks of life to prevent 82Q overexpression and then removed dox to resume 82Q overexpression for 6 weeks (82Q 6OFF-6ON), 12 weeks (82Q 6OFF-12ON) and 18 weeks (6OFF-18ON). We assessed mouse motor performance using an accelerating rotarod and immunohistochemical detection of Calbindin and vesicular Glutamate Transporter 2 to assess PN structure and climbing fibre (CF) synaptic inputs respectively. Twelve week old SCA1 82Q ON mice showed significant deficits in motor performance (two-way-ANOVA, $P<0.01$) and shrunken PN dendrites with stunted climbing fibres (CFs) (one-way ANOVA, $P < 0.0001$). In contrast, 82Q 6OFF-6ON and 82Q 6OFF-12ON mice where 82Q expression was prevented early in life and then turned back on, performed normally (2-way-ANOVAs, $P>0.1$). 82Q 6OFF-18ON mice showed mild motor impairment (two-way-ANOVA, $P = 0.07$) but remarkably, PNs and CFs were normal in all dox-repressed SCA1 mice (one-way ANOVA, $P > 0.2$). Our results indicate that the developing cerebellum is highly vulnerable to 82Q overexpression and emphasize the importance of treating SCA1 early in life.

Poster 5.2

Can brief exposure time (Under 170ms) of faces evoke N170?

H. JIN, P. CORBALLIS, M. OXNER, and W. G. HAYWARD
School of Psychology, University of Auckland, Auckland, New Zealand

Plenty of studies have found that faces will evoke a particularly large negative impulse peaking at around 170ms after the onset of face stimuli, which is known as N170. However, it is unknown that whether brief exposure time that is under 170ms still can elicit N170. Twenty participants (13 females, 22.2±4.6 years old) were recruited for an electroencephalography (EEG) study, in which face and house images were presented for 17ms, 50ms, 100ms, and 200ms on the monitor and the participants were asked to judge if the image was a face or a house by pressing keys. During the whole experiment, scalp EEG activity was recorded with a 128 channel scalp. Results showed that, consistent with the previous studies, the amplitude of N170 on occipitotemporal sites (P7, PO7, P8, PO8) for face images is larger than that for house ones. Also, the amplitude of N170 on right hemisphere (P8, P08) is larger than that on left hemisphere (P7, PO7). The most interesting result is that there were no differences between the amplitude of N170 evoked by faces for different exposure time, suggesting that very brief presentation of face images can still evoke N170. This study may indicate that a very short presentation of faces is enough to elicit the brain to process them.

Poster 5.3

Massively parallel simulations of neurovascular coupling with nitric oxide pathway and extracellular diffusion

A. KENNY, T. DAVID, and M. PLANK
University of Canterbury High Performance Computing, University of Canterbury, Christchurch, New Zealand

The cerebral vasculature is able to regulate perfusion in response to local changes via the process of neurovascular coupling (NVC), an intercellular communication system between neurons, glial cells and vascular cells comprising a neurovascular unit (NVU). NVC is characterised by an increase in neuronal activity followed by a rapid dilation of blood vessels and increased localised blood supply. In order to model NVC with a high spatial and temporal resolution our research group has developed a numerical model able to describe the vascular response to neuronal stimulation and validated with experimental results. The model consists of large numbers of NVUs embedded in a "tissue like" structure coupled to a space filling H-tree simulating the vasculature. Numerical procedures are implemented in parallel making it possible to globally couple thousands of NVUs to the vascular tree and to each other via extracellular ion diffusion. The model is able to regulate the local dilation of the vascular tree in response to neuronal input. This input results in the relaxation of the smooth muscle cells leading to vessel dilation. The extracellular ion diffusion between NVUs results in a physiologically realistic gradient of vessel radius and blood flow from the area of stimulation to non-stimulation while still remaining sufficiently localised over larger time scales. Implementing the nitric oxide (NO) signalling pathway with synaptic glutamate input results in a large increase in vessel dilation with a slow return to resting state after stimulation is removed. NVUs adjacent to the stimulated area receive an influx of extracellular potassium, but as their NO pathways remain inactivated this only induces weak dilation with a fast return to the resting state.

Poster 5.4

Continuous exposure to valproate during prenatal development as an animal model for autism spectrum disorder

M. A. PETTIE
School of Psychology, Victoria University of Wellington, Wellington, New Zealand

Autism spectrum disorder (ASD) is a complex lifelong condition, characterised by three core deficits in social interaction, communication and repetitive behaviours (Levy, Mandell, & Schultz, 2009). Genetic and environmental components are known to contribute to the aetiology of ASD. An environmental influence linked with ASD is Valproic Acid (VPA). This is an anticonvulsant and prenatal exposure to this compound is linked with cognitive and developmental deficits (Roullet et al 2013; Lloyd. 2013), also a 4.42% increased risk for ASD (Rasalam, 2005). The prenatal exposure of VPA has also been used to generate an animal model of ASD (Rodier et al. 1997). The current method utilises a single injection on gestation day 12.5 which results in behaviour deficits in the offspring, aligning with deficits found in ASD. However, the single injection does not equate to the repeated exposures a human would take during pregnancy. As such, this study investigates the effects of continuous prenatal exposure to VPA in rats to examine alterations in social cognition through changes in the ultrasonic vocalizations, scent marking and play behaviour; along with a measure of cognitive flexibility through a spatial learning task. The extent of detrimental effects will correlate with the dosage administered to the dams. Overall, this study improves the current animal model for ASD through the continuous exposure of VPA and examined with multiple behaviour measures.

Poster 5.5

Temporal and regional onset of leptin resistance in diet induced obese mice

M. Z. RIZWAN[1,2], N. SKINNER[2], S. MEHLITZ[2], and A. TUPS[2]

[1]Department of Anatomy, [2]Department of Physiology, Brain Health Research Centre and Centre for Neuroendocrinology, University of Otago, Dunedin, New Zealand

Leptin, an adipocyte hormone that is produced in proportion to body fat levels, primarily acts to regulate body weight. In common forms of obesity, leptin levels are high correlating positively with adiposity. This condition, termed leptin resistance, is present in 95% of obese individuals. Leptin resistance was considered to be restricted to the arcuate nucleus (ARC) and to only occur after differences in body weight were well established (after 6 days). Here, we explored whether leptin resistance occurs earlier (e.g. after 4hr or 24hr), as well as 10d and 28d, and also in other hypothalamic regions. Mice were exposed to either a low- (LFD) or high- (HFD) fat diet for the four different durations. At their respective time-point, they received an intraperitoneal injection of either vehicle (PBS) or recombinant mouse leptin (1.25mg/kg), and the number of phosphorylated signal transducer and activator of transcription-3 (pSTAT3; marker for leptin sensitivity) immunoreactive cells in the ARC, ventromedial (VMH) and dorsomedial (DMH) hypothalamus were analysed. In the ARC, within 24hr of HFD feeding the number pSTAT3-immunoreactive cells declined by 40% ($p<0.01$), which was similar to 10d. However, after 28d, pSTAT3-immunorecative cell number declined further to similar levels as control, indicating leptin resistance. In both the VMH and DMH, a 50% reduction in pSTAT3-immunoreactive cells ($p<0.05$) was observed after 24hr followed by further reduction after 10d. Surprisingly, after 28d there was a significant increase in pSTAT3-ir cells ($p<0.05$), indicating partial recovery of leptin sensitivity. These findings demonstrate that HFD-induced leptin resistance occurs before changes in body weight and is not confined to the ARC.

Poster 5.6

Moderate exercise does not alter the neurogenic niches in sheep

M. E. V. SWANSON[1], E. C. FIRTH[2], and M. A. CURTIS[1]

[1]Department of Anatomy and Medical Imaging, [2]Department of Sport and Exercise Science, University of Auckland, Auckland, New Zealand

Neurogenesis and progenitor cell proliferation primarily occur in the subventricular zone (SVZ) and the subgranular zone (SGZ) in the adult human brain. Recently, rodent studies have demonstrated that exercise can increase neurogenesis; however, it is unclear if exercise also has this effect in more complex mammalian brains. The overarching aim of this study was to explore whether exercised-induced neurogenesis occurs in larger mammalian brains more representative of humans. Bromodeoxyuridine (BrdU), a thymidine analogue that is incorporated into the DNA of proliferating cells, was injected into twelve sheep; the six in the exercise group ran for 30 minutes a day over five days, while the remaining six were the non-exercise controls. BrdU-positive cells in the SVZ and SGZ were immunostained, imaged and counted for comparison. Immunofluorescence was used to triple label BrdU with neuronal and glial markers to analyze changes in maturation kinetics with exercise. Overall, no significant change in the number or distribution of BrdU-positive cells was observed in the sheep SVZ and SGZ with exercise. Immunofluorescent triple labelling showed no co-labelling of BrdU with mature neuronal or glial markers in the exercised and non-exercised sheep SVZ and SGZ. The non-significant changes in BrdU-positive cell distribution and number in the sheep neurogenic niches with exercise is not in keeping with results from exercise-based studies in rodents. There is no evidence from the current study to suggest that exercise at the levels administered increases neurogenesis or cell proliferation in young sheep, but this first set of studies has been helpful for informing future exercise trials in large animals.

Poster 5.7

Changes in alpha5 subunit containing GABA A receptors in the human Alzheimer's disease hippocampus

B. G. CALVO-FLORES[1], H. J. WALDVOGEL[1], B. J. L. SYNEK[1,2], C. TURNER[1,2], R. L. FAULL[1], and A. KWAKOWSKY[1]

[1]Centre for Brain Research, Department of Anatomy and Medical Imaging, University of Auckland, Auckland, New Zealand

[2]Department of Anatomical Pathology, LabPlus, Auckland City Hospital, Auckland, New Zealand

Alzheimer's disease (AD) is a neurodegenerative disorder affecting millions of people worldwide. Currently there is no effective treatment to cure, delay, or to stop the progression of the disease. Gamma-aminobutyric acid, GABA, is the main inhibitory neurotransmitter in the central nervous system and has a critical role in regulating neuronal excitability and information processing in the brain. GABA receptors are formed by pentameric assembly of multiple subunits. Alpha5 subunit containing GABA A receptors (GABARα5s) are highly expressed in the hippocampus and are very sensitive to low concentrations of ambient GABA. Their continuous activation generates a tonic hyperpolarizing conductance and the modulation of tonic activity is one of the potential targets of GABAergic drugs in the AD brain. This study is the first to show the detailed expression of the GABAR α5 subunits in the human hippocampus at the protein level. We have also examined the regional and layer specific distribution of the GABAR α5 subunits in control and AD human hippocampal tissue samples using free-floating immunohistochemistry and confocal microscopy. The dentate gyrus exhibited the highest density of α5 subunits. The CA1-CA3 pyramidal neurons and their dendritic tree showed a high level of immunolabeling as well. We found a significant increase of the $GABA_A$Rα5 subunits in the stratum oriens and stratum pyramidale in the hippocampal CA1 region and subiculum. In conclusion, these findings suggest that the GABARα5s are well preserved in the AD hippocampus. Therefore, targeting the GABARα5s is opening a promising pharmacological treatment for AD by modulating the dynamic balance of excitatory/inhibitory pathways. The regulation of network excitability may contribute to $GABA_A$R-α5 regulation of hippocampus-dependent behavioural processes, such as aspects of learning and memory.

Poster 5.8

5-HT antagonists fail to alter MDMA self-administration in rats

J. FOOTE

School of Psychology, Victoria University of Wellington, Wellington, New Zealand

Acute exposure to ±3,4-methylenedioxymethamphetamine (MDMA) preferentially increases release of serotonin (5-HT), and a role of 5-HT in many of the behavioral effects of acute exposure to MDMA has been demonstrated. A role of 5-HT in MDMA self-administration in rats has not, however, been adequately determined. Therefore, the present study measured the effect of pharmacological manipulation of some 5-HT receptor subtypes on self-administration of MDMA. Rats received extensive experience with self-administered MDMA prior to tests with 5-HT ligands. Doses of the 5-HT1A antagonist, WAY 100635 (0.1-1.0 mg/kg), 5-HT1B antagonist, GR 127935 (1.0-3.0 mg/kg), and the 5-HT2A antagonist, ketanserin (1.0-3.0 mg/kg) that have previously been shown to decrease self-administration of other psychostimulants and that decreased MDMA-produced hyperactivity in the present study did not alter MDMA self-administration. Experimenter-administered injections of MDMA (10.0 mg/kg, ip) reinstated extinguished drug-taking behaviour, but this also was not decreased by any of the antagonists. In contrast, both WAY 100635 and ketanserin, but not GR 127935, decreased cocaine-produced drug seeking in rats that had been trained to self-administered cocaine. The 5-HT1A agonist, 8-OHDPAT (0.1-1.0 mg/kg), but not the 5-HT1B/1A agonist, RU 24969 (0.3-3.0 mg/kg), decreased drug-seeking produced by the reintroduction of a light stimulus that had been paired with self-administered MDMA infusions. These findings suggest a limited role of activation of 5-HT1A, 5- HT1B or 5-HT2 receptor mechanisms in MDMA self-administration or in MDMA-produced drug-seeking following extinction. The data suggest, however, that 5-HT1A agonists inhibit cue-induced drug-seeking following extinction of MDMA self-administration and might, therefore, be useful adjuncts to therapies to limit relapse to MDMA use.

Poster 5.9

Atypical matter pathways in BDNF mutation carriers

N. S. MCKAY and I. J. KIRK
School of Psychology, University of Auckland, Auckland, New Zealand

A common single nucleotide polymorphism (SNP) within the gene for brain derived neurotrophic factor (BDNF) is known to impact both brain structure and memory performance. While previous studies have found clear behavioural differences on recognition memory tasks, and structural differences in hippocampal volumes, little research has focused on how this mutation might impact white matter structures. In the current study we therefore compare behavioural performance on recognition memory tasks, and use diffusion weighted images to look at white matter pathways that underlie recognition memory processes. Recognition memory is comprised of two subcomponents, familiarity and recollection, that are dependent upon related but distinct neural circuits. The network that underlies processing of familiarity-based recognition judgments is dependent upon the medial dorsal thalamic nucleus, while the anterior thalamic nucleus has been linked to the circuit that underlies recollection-based processing. In the present study carriers of at least one copy of the BDNF SNP were compared with non-carriers on two recognition memory tasks. Connectivity analyses were conducted to determine whether differences exist in white matter connectivity across familiarity- or recollection-associated tracts seeded from the relevant thalamic nuclei. No performance differences were observed between SNP carriers and non-carriers on either recognition memory task. However, connectivity differences were found across both familiarity- and recollection-associated tracts: carriers of the BDNF SNP displayed lower connectivity compared to non-carriers. This result is consistent with the findings of previous studies that have shown carriers of the BDNF SNP to perform worse on memory tasks, and to have abnormal gray matter structure. We suggest that the white matter microstructural differences reported here, might help to explain the mechanism through which behavioural differences might occur in these two genetic groups.

Poster 5.10

Effect of circadian rhythms on leptin sensitivity

N. SKINNER, M. Z. RIZWAN, and A. TUPS
Centre for Neuroendocrinology, Brain Health Research Centre, Department of Physiology, University of Otago, Dunedin, New Zealand

Metabolic processes are tightly regulated by the central circadian clock, which resides in the suprachiasmatic nucleus of the hypothalamus. Food intake and metabolism are controlled by the hormone leptin which is secreted by adipocytes. Paradoxically, in common forms of obesity, as adipose tissue mass increases, circulating leptin levels rise and fail to suppress appetite, leading to the development of leptin resistance. It is unknown as to whether leptin resistance is caused by high fat diet (HFD) or secondary to changes in body weight. In this study we investigated whether disruptions in the circadian rhythm affect leptin sensitivity and important metabolic markers, and whether they are altered by exposure to HFD. To alter the circadian rhythm in mice, the usual 12h light/12h dark light cycle was shifted forward by 6h every 6 days (comparable to a 6 hour jetlag flying east). This treatment led to an increase of body weight in mice on low fat diet (LFD) compared with mice on a constant 12h light/12h dark light cycle, whereas on HFD no difference occurred. Leptin sensitivity was assessed by the ability of leptin to activate its transcription factor (signal-transducer and activator of transcription) in the arcuate nucleus, the key site of leptin action in the central nervous system. Interestingly, we discovered that leptin sensitivity was reduced by circadian disruption within the ARC. This effect was independent of either the LFD or HFD, suggesting that leptin resistance is not caused by an increase in body weight per se. It appears rather that the circadian clock is a primary driver of alterations in leptin sensitivity.

Poster 5.11

Cerebrovascular expression of GABA signalling components in the medial temporal gyrus of healthy and Alzheimer's disease brains

K. GOVINDPANI[1], B. J. L. SYNEK[1,2], C. TURNER[1,2], H. J. WALDVOGEL[1], R. L. FAULL[1], and A. KWAKOWSKY[1]
[1]Centre for Brain Research, Department of Anatomy and Medical Imaging, University of Auckland, Auckland, New Zealand
[2]Department of Anatomy and Anatomical Pathology, LabPlus, Auckland City Hospital, Auckland, New Zealand

Cerebrovascular dysfunction is strongly associated with the pathogenesis of AD, often preceding the onset of clinical symptoms. The inhibitory neurotransmitter GABA can regulate cerebrovascular function, controlling vasoconstriction and blood flow – however the mechanisms underlying this are poorly understood. The GABA signalling system displays a high degree of structural heterogeneity, comprising $GABA_A$ and $GABA_B$ receptors, transporters, and synthesising and metabolising enzymes. AD-associated alterations in the expression of some GABA signalling components have previously been reported in certain brain regions. We have carried out an investigation into AD-associated changes in the cerebrovascular expression of a number of GABA signalling components, utilising fluorescence immunohistochemistry and confocal imaging. Tissue was obtained from the medial temporal gyri of 7 healthy and 7 age-matched AD patients. Here we report for the first time the expression of a number of GABA signalling components, including the alpha2, alpha3, beta1, beta2, beta3, and gamma2 $GABA_A$ receptor subunits, the GAD67 synthesising enzyme, and the GAT1, GAT3 and BGT1 transporters, on endothelial cells of the human cerebral vasculature. The alpha2, beta1, and beta2 $GABA_A$ receptor subunits were only expressed at low levels. The alpha1 subunit was not found to be expressed on these cells. No significant differences were observed in the cerebrovascular expression of these GABA signalling components between healthy and AD brains. In summary, $GABA_A$Rs display a unique subunit composition in the cerebral vasculature and are relatively well preserved in AD.

Poster 5.12

In vivo tolerability and effects of autophagy enhancers as potential therapeutic interventions for Alzheimer's disease

S. A. MERCER[1, 2], M. Y. I. CHEONG[2], W. C. ABRAHAM[1], and S. M. HUGHES[2]
[1]Department of Psychology, [2]Department of Biochemistry, Brain Health Research Centre, Brain Research New Zealand, University of Otago, Dunedin, New Zealand

Dysfunction in the autophagy-lysosomal pathway has been implicated in Alzheimer's disease (AD) pathophysiology. In mouse models, enhancement of autophagy through transcription factor EB (TFEB), a "master regulator" of genes for lysosomal biogenesis and autophagy, reduces plaque pathology and partially reverses behavioural deficits. Recently, pharmaceutical agents such as Captisol (sulfobutylether β-cyclodextrin) and fibrates (Gemfibrozil and Fenofibrate), approved for clinical use in other indications, were found to increase brain levels of TFEB and downstream markers of autophagic function, although the doses required to achieve this effect chronically *in vivo* are not known. Hence, the present study aimed to first examine the tolerability of these three drugs in wild-type mice and examine whether these doses were sufficient to elevate autophagy. Mice were administered orally a low or medium dose of one drug twice daily, three times per week for four weeks. There were no qualitative pathological changes to the kidneys or liver across the treatment groups, or any other evidence of drug intolerability. In the brain, increased levels of SQSTM1 were noted in dorsal cortical, hippocampal and thalamic regions across all treatment groups irrespective of dose, relative to vehicle controls (repeated measures ANOVA: Treatment $F[6, 17] = 2.98$, $p<0.05$), indicating potentially increased targeting of cellular waste. TFEB protein levels and localisation, and markers of autophagosome-lysosome fusion (LAMP-2), and substrate degradation (Cathepsin D) will also be examined to determine effects across the autophagic process. The drug and dose that best enhances autophagy will be tested for therapeutic efficacy in a mouse model of AD.

Poster 5.13

Greater activity in the salience network of people with schizophrenia who respond to first-line antipsychotics

B. R. RUSSELL[1,2], M. E. McILWAIN[1], V. ANDERSON[1], R. R. KYDD[3], and C. B. McNABB[1]
[1]National School of Pharmacy, University of Otago, Dunedin, New Zealand
[2]School of Pharmacy, [3]Department of Psychological Medicine, University of Auckland, Auckland, New Zealand

Clinical response to antipsychotic medication is variable in people with schizophrenia (PWS). There is no current method to predict which antipsychotic will be most effective for an individual. Using functional magnetic resonance imaging (fMRI), we aimed to identify biomarkers of treatment response in PWS who were receiving first-line antipsychotics (FLR), clozapine monotherapy (CLOZ) or augmented antipsychotic drug therapy (AUG) following treatment failure with FLR and CLOZ. Forty-seven PWS (17 FL; 16 CLOZ; 14 AUG) and 15 healthy controls underwent structural and resting-state functional MRI scans on a Siemens Skyra 3T scanner. All PWS were receiving medication at the time of scanning. Pre-processing of images was carried out using FSL. Main effects and group differences in functional activity were assessed using a one-way ANOVA following independent components analysis (ICA) in FSL's MELODIC. Thirty six independent components were selected for comparison, of which one (the salience network) demonstrated statistically significant differences between FLR and healthy and CLOZ groups. Within this network, FLR demonstrated greater activation than CLOZ and healthy controls. These data demonstrated increased activity in the salience network of FLR compared to those receiving CLOZ or healthy controls. These findings support a hypothesis that schizophrenia may be divided into subcategories based on treatment response and that PWS who respond to first-line antipsychotics may represent a functionally distinct subtype of the disorder.

Poster 5.14

Single and combined lesions of different limbic thalamic nuclei: influence on random foraging in the radial arm maze

J. J. HAMILTON[1,2], B. A. L. PERRY[1,2], S. C. BARNETT[1,2], and J. C. DALRYMPLE-ALFORD[1,2,3]
[1]Department of Psychology, [2]Brain Research New Zealand, University of Canterbury, Christchurch, New Zealand
[3]New Zealand Brain Research Institute, Christchurch, New Zealand

Goal-directed searching, measured by random foraging in complex spatial environments, is dependent on intact ventral hippocampal-ventral pallidal pathways. The influence of neurotoxic thalamic lesions on this spatial behaviour is unknown. We compared the effects of bilateral anteroventral (AV), mediodorsal (MD) and a combination of unilateral lesions to these two nuclei on a random foraging task in the radial arm maze (RAM) in which the 48 rats were required to find food rewards in 4/8 randomly baited arms across 14 daily sessions. AV lesions were expected to impair random foraging due to their reciprocal connections with the ventral hippocampal formation; MD lesions were expected to influence this task because the MD provides an interface between the ventral pallidum and the prefrontal cortex. A disconnection lesion across the AV and MD (unilateral lesions; Contra) tested the potential impact of the AV and MD working in concert for accurate random foraging, when compared to ipsilateral lesions (Ipsi) to these two sites. All 5 groups showed improved performance across sessions, but the AV group made significantly more errors, to both baited and unbaited arms, than the Sham and Ipsi groups, while the MD and Contra groups showed intermediate levels of performance. This new evidence suggests that the AV - ventral hippocampal interactions play a more significant role in goal directed spatial searching behaviour than does the MD - ventral pallidal outputs.

Poster 5.15

Cognitive language difficulties in a tumour population: Three month follow-up

K. FOWLER [1], C. WILSHIRE [1], and A. PARKER[2]

[1]Department of Psychology, Victoria University of Wellington, Wellington, New Zealand

[2]Wellington Hospital, Wellington, New Zealand

Much is known about language and related cognitive functions following stroke, yet few studies have examined other aetiologies, such as neurological tumours. This study examined patients who had undergone tumour surgery at least three months previously. Drawing on recent cognitive theory, we identified and measured a set of "core" cognitive skills that are necessary for communication and for effective cognitive function more generally. For example, the core language skills measured included: accessing semantic knowledge, phonological encoding, verbal short-term memory and, goal-driven lexical selection. The core higher cognitive skills included processing speed, sustained attention, monitoring, and (verbal and nonverbal) inhibitory control. Our aims were: (a) to assess language and higher cognitive function in post-acute tumour surgery patients; (b) evaluate language change when compared to pre-operative and acute postoperative periods. Twenty six neurological tumour patients were assessed 3 months post-operatively on the entire protocol. During this follow-up testing phase, many patients were significantly impaired on one or more of the core language skills. This suggests that significant language impairments are likely to persist well beyond the acute surgical stage. Pre and post-operative language skills were a significant predictor of performance at follow up. Patients' performance on tasks involving verbal control was not predictive of their performance on the corresponding nonverbal tasks. This finding suggests that cognitive control processes are highly domain specific. With respect to more general cognitive skills, many patients showed isolated deficits involving just one skill. This finding supports models that propose a high degree of functional specialisation within the prefrontal cortex.

Poster 5.16

Pre-exposure to MDMA facilitates the acquisition of MDMA self-administration: Role of dopamine D2 receptors

R. VAN DE WETERING and S. SCHENK

School of Psychology, Victoria University of Wellington, Wellington, New Zealand

The dopaminergic mechanisms underlying the development of behavioral sensitization have been suggested to contribute to the formation of excessive drug-taking and drug seeking behavior. *Objectives.* The purpose of this study was to investigate the effect of a sensitizing regimen of MDMA exposure on the subsequent acquisition of MDMA self-administration by rats and to determine the role of dopamine D_2 receptor mechanisms. Rats were surgically implanted with intravenous jugular catheters before receiving daily injections of the selective D_2 antagonist, eticlopride (0.0, 0.3 mg/kg, i.p.) and MDMA (0.0, 10.0 mg/kg, i.p.) during a five-day pre-treatment regimen. Two days following the final pre-treatment session, rats were tested for acquisition of MDMA self-administration. Pre-treatment with MDMA facilitated the acquisition of MDMA self-administration. Co-administration of eticlopride during MDMA pre-treatment failed to significantly attenuate this effect. Interestingly, pre-treatment with eticlopride alone also facilitated the acquisition of self-administration. These findings suggest that repeated MDMA exposure sensitized rats to the reinforcing effects of MDMA. D_2 receptor activation was not required for the development of sensitization to the reinforcing effects of MDMA induced by pre-treatment, despite previous findings demonstrating a critical role of D_2 receptors in the development of locomotor sensitization to MDMA, which suggests the involvement of other mechanisms. Repeated eticlopride administration can produce a homeostatic upregulation of D_2 receptors, suggesting a potential mechanism for the facilitated acquisition of MDMA self-administration produced by eticlopride pre-treatment alone.

Poster 5.17

Investigation of GABA signalling in an in-vivo Alzheimer's disease mouse model

T. H. PALPAGAMA[1], W. P. TATE[2], H. J. WALDVOGEL[1], R.L. FAULL[1], and A. KWAKOWSKY[1]
[1]*Centre for Brain Research, Department of Anatomy and Medical Imaging, University of Auckland, Auckland, New Zealand*
[2]*Department of Biochemistry, University of Otago, Dunedin, New Zealand*

GABA is the main inhibitory neurotransmitter of the central nervous system. Changes in the GABAergic systems have been identified in the progression of Alzheimer's disease (AD). GABA is synthesized by glutamic acid decarboxylase (GAD), packaged in vesicles through vesicular GABA transporter (VGAT), and acts on $GABA_A$ and $GABA_B$ receptors. GABA clearance relies on GABA transporters, GAT-1, GAT-3 and BGT-1, and is metabolised by GABA transaminase (ABAT). AD is characterized by accumulation of neurotoxic beta-amyloid (Aβ) and impaired cognitive function. In this study, we have characterised molecular changes of GABA signalling components in the hippocampal CA1 and dentate gyrus (DG) of aged male wild-type mice that received bilateral $Aβ_{1-42}$ injection into the CA1 region of the hippocampus. 3 days after $Aβ_{1-42}$ administration, prior to cell loss, the hippocampal CA1 and DG regions were dissected for Western blotting. We found a significant increase in the expression level of the $GABA_A$ receptor subunit alpha1 in the CA1 hippocampal region of the $Aβ_{1-42}$ treated mice as compared with naïve control or artificial cerebrospinal fluid (ACSF) injected control mice. In the CA1 and DG no significant changes were identified in the expression level of other GABA signalling components, GADs, GATs, alpha2,3,5, beta1,2,3, gamma2 $GABA_A$ and R1 and R2 $GABA_B$ receptor subunits along with alpha 1 in the DG. These results suggest that the GABAergic system is relatively well preserved prior to $Aβ_{1-42}$ -induced cell loss in this *in vivo* AD model. However, the alpha1 containing $GABA_A$ receptor function might be seriously affected and this could influence function of the $GABA_A$Rs and GABAergic inhibition within the hippocampus.

Poster 5.18

Habitual physical activity levels, the P300 and the significance of alpha power

N. E. TAYLOR, D. MOREAU, and P. M. CORBALLIS
School of Psychology, University of Auckland, Auckland, New Zealand

Age-related declines in cognitive function are a major cause for concern in public health. Accordingly, there is considerable interest in developing lifestyle or exercise interventions that can prevent or delay the onset of cognitive decline. The relationship between the P300 component of the event-related potential (ERP) and levels of habitual physical activity has been well established, and offers a potential marker for cognitive function. However, there are still large underlying questions that remain about the nature of this relationship. This study aims to determine the links between levels of psychophysiological measures such as central blood pressure, heart rate, executive function and resting EEG, in order to reveal how habitual physical activity levels affect the P300. Electrophysiological effects of physical activity were investigated in a cross-section study comparing two groups of people who vary in habitual levels of physical activity. The International Physical Activity Questionnaire was used to classify participants into two groups – "high-active" or "inactive", based on overall levels of activity. Central blood pressure and heart rate were also measured to establish a link between self-reported physical activity levels and physiological function. ERPs were recorded during the AX-Continuous Performance Task in order to extract P300 responses to stimuli requiring cognitive control. Preliminary data suggest that P300 amplitude and latency were both affected by physical activity. Furthermore, the variation in P300 between groups was modulated by differences in resting EEG alpha power between groups. While preliminary, these findings imply that cognitive control may be influenced by physical activity, and suggest an additional approach for researchers to consider when investigating how exercise interventions can influence brain health and cognitive function.

Poster 5.19

Pericyte immunosuppression in glioblastoma multiforme

M. O. JORET, T. I-H. PARK, P. SCHWEDER, E. MEE, B. J. H. KIM, R. L. M. FAULL, and M. DRAGUNOW
Center for Brain Research, University of Auckland, Auckland, New Zealand

Glioblastoma multiforme (GBM) is the most common and fatal type of primary malignant brain cancer in adults. Tumor microenvironment immunosuppression is a hallmark of the disease and GBM is interestingly less likely to occur in people with brain disorders associated with immunoactivation such as Alzheimer's disease. Current research to better understand GBM-mediated immunosuppression has focused on tumor cells, tumor associated microglia and macrophages, as well as endothelial cells, leaving pericytes largely unstudied. To probe for differences in immune phenotype, GBM pericytes (GBMP) and normal human brain tissue pericytes (NHBTP) were isolated and cultured from surgically excised samples donated by consenting patients undergoing tumor resections at Auckland City Hospital. Following treatments with differential concentrations of pro-inflammatory cytokines, cultured cells were stained for inflammatory markers using fluorescent immunocytochemistry techniques and were subsequently imaged. NHBTP expression of intercellular adhesion molecule 1 and monocyte chemoattractant protein 1 was two times more elevated than that of GBMP when treated with interleukin 1β (IL1B) at a concentrations of 0.1 ng/ml or higher ($p < 0.0001$). Additionally NHBTP expressed significantly higher levels of interferon gamma induced protein 10 compared to GBMP when treated with 1 ng/ml of IL1B or higher ($p < 0.0001$). Similar results were obtained with interferon γ treatment. Our study shows that patient-matched GBMP and NHBTP have different immune phenotypes, highlighting a possible role for pericytes in GBM tumor microenvironment immunosuppression. Understanding the underlying mechanisms of immunosuppression in GBM may provide insights into GBM targeted immunotherapy and suppressing pericyte-mediated brain inflammation in neurodegenerative disorders.

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Poster 5.20

Development of in vitro models to measure the effects of plant metabolites on neuronal mitochondrial function

J. Y. NG[1,2,3], A. J. HICKEY[1], D. L. CHRISTIE[1,2,3], A. SCHEEPENS[4], and N. P. BIRCH[1,2,3]
[1]School of Biological Sciences, [2]Centre for Brain Research, [3]Brain Research New Zealand, University of Auckland, Auckland, New Zealand
[4]Plant and Food Research Limited, Auckland, New Zealand

Mitochondrial dysfunction in the human brain has been implicated in processes of aging and is a key event in the pathophysiology of neurodegenerative diseases including Parkinson's disease and Alzheimer's disease. Several lines of evidence suggest that phytochemicals and more importantly, their bioavailable plasma metabolites may be able to rescue dysfunctional mitochondria in *in vivo* and *in vitro* models of brain disease. We aim to determine the effect of a range of phytochemicals and their plasma metabolites at physiologically relevant concentrations for the rescue of neuronal mitochondrial dysfunction. To prepare for these experiments, we have established two *in vitro* models using the human SH-SY5Y cell line: undifferentiated SH-SY5Y cells, presenting a dopaminergic phenotype (as a model for Parkinson's disease) and cells differentiated with retinoic acid, presenting a cholinergic phenotype (as a model for Alzheimer's disease). Mitochondrial dysfunction was induced with rotenone, an inhibitor of Complex I in the electron transport chain. High-resolution respirometry studies demonstrated that rotenone reduced respiration in both cell models. Rotenone also decreased mitochondrial activity (MTT assay). At 50 µM rotenone, mitochondrial activity decreased by 75.5 ± 8.0%. in undifferentiated cells and by 44.3 ± 5.1% in differentiated cells. β-Amyloid$_{1\text{-}42}$ is also being used to induce mitochondrial dysfunction. Oligomeric and fibrillar forms of β-Amyloid$_{1\text{-}42}$ were characterised by transmission electron microscopy and Western blotting. Treatment experiments with oligomeric β-Amyloid$_{1\text{-}42}$ are in progress. Finally, both cell models were treated with resveratrol, a well studied plant compound that regulates mitochondrial function. Low concentrations of resveratrol increased mitochondrial activity in undifferentiated cells, suggesting resveratrol may stimulate mitochondrial biogenesis at low concentrations.

Poster 5.21

Dynamic hippocampal, orbitofrontal and subthalamic oscillations in rats performing a stopsignal task

A. BANSTOLA, C. K. YOUNG, and N. McNAUGHTON
Department of Psychology, University of Otago, Dunedin, New Zealand

Brain oscillations can be used to decode normal and pathological brain function. From the production of simple motor responses to the control of goal-directed actions, synchronous rhythmic activity appears to be important. The Stop Signal Task (SST) modulates rhythmic activity in the right frontal area of humans as a result of activation of the behavioural inhibition system. Frontal cortical lesions and manipulations to the subthalamic nucleus negatively impact on SST performance. There is evidence that the hippocampus may provide contextual and/or error monitoring information to the frontal-subthalamic axis. There are currently no studies of non-human subjects that record brain oscillations concurrently from the hippocampus, subthalamic nucleus and orbitofrontal cortex in rats engaged in voluntary behaviours as well as goal directed behaviours in the SST. We simultaneously recorded local field potentials from the hippocampus, orbitofrontal cortex and subthalamic nucleus in rats performing a SST. Event-triggered spectral analysis, identified three frequency bands of interest during the "Go" trials: 8-12 Hz, 15-25 Hz and 30-40 Hz. As assessed with coherence analysis, OFC-STN interactions appeared most prominent in the 8-12 Hz and 15-25 Hz range, while HPC-OFC interactions were clearest in the 8-12 Hz range throughout SST. HPC-STN interactions also occurred in the 30-40 Hz range. Our data currently suggest similar changes in oscillatory interactions between HPC, OFC and STN when a rat is performing a motor response to a cue, but markedly different changes following reward delivery. We expect the "Stop" signal will elicit an increase in OFC-STN interactions while HPC involvement will depend on the success or failure to correctly inhibit ongoing action.

Poster 5.22

Maternal immune activation alters immunoreactive profiles of nNOS-containing neurons and microglia in postnatal day 2 rat brains

J. ZHANG[1,4], Y. JING[1,4], H. ZHANG[2,4], D. K. BILKEY[3,4], and P. LIU[1,4]
[1]Department of Anatomy, [2]School of Pharmacy, [3]Department of Psychology, [4]Brain Health Research Centre, University of Otago, Dunedin, New Zealand

Prenatal brain maldevelopment and microglia dysfunction have been implicated to the development of schizophrenia. A number of behavioral and neural features of schizophrenia are evident in the maternal immune activation (MIA) offspring. Previous research has shown altered metabolism of L-arginine, an amino acid with several bioactive molecules, in the juvenile and adult rat MIA offspring. However, it is unclear how MIA affects brain arginine metabolism during the early developmental stage. The present study investigated how MIA induced by a single systemic administration of the synthetic cytokine inducer polyinosinic–polycytidilic acid during mid-gestation (GD15) affected the immunohistochemical profiles of neuronal nitric oxide synthase **(**nNOS**)** and microglia in the rat brains at age of postnatal day 2 (equivalent to human 26-30 gestational weeks). In this pilot study, we found markedly increased number of nNOS-positive neurons in the striatum in the MIA group relative to the control group (n=4/group from 4 litter groups). A few nNOS-positive neurons were seen in the hippocampus in the MIA, but not the control, group. Moreover, we observed delayed microglia maturation, as well as migration, in MIA offspring. These preliminary observations, for the first time, demonstrate that a single MIA insult leads to aberrant expression of nNOS and abnormal microglia development at age of postnatal day 2. These changes may contribute to neuronal dysfunctions and behavioural phenotypes observed in the juvenile and adult MIA offspring.

Poster 5.23

Individual working memory performance is predicted by a neural index of distractor disengagement

D. T. HENARE and P. M. CORBALLIS

School of Psychology and Centre for Brain Research, University of Auckland, Auckland, New Zealand

While working memory and selective attention have traditionally been viewed as distinct processes in human cognition, there is now a growing body of literature which demonstrates significant overlap between these two constructs. One line of evidence for the presence of this relationship comes from between-subject designs in which individuals low in working memory capacity show greater interference in standard attention-based tasks. The specific neural mechanisms involved in this interaction are still unknown, however three lateralised ERP components have been identified as ideal candidates for studying the neural underpinnings of attention processes. N2pc, Ptc, and SPCN have been associated with object selection, attentional disengagement, and short term maintenance of target features respectively. In this study we measured these components during the delay period of a working memory task in order to see whether they could predict performance on the working memory task. The results showed that individuals who produce a larger Ptc during visual search are predicted to perform faster and more accurately on the working memory task. They also demonstrate that the strength of this effect is modulated by the presence of distraction in the working memory task. These results suggest that individual differences in working memory performance are specifically related to individual differences in the ability to disengage from distraction, and that the presence of distraction during working memory encoding effects subsequent visual search performance.

Poster 5.24

Absolute number of parvicellular and magnocellular neurons in the red nucleus of the rat midbrain: A stereological study

D. E. OORSCHOT and B. E. AGHOGHOVWIA

Department of Anatomy, Brain Health Research Centre, University of Otago, Dunedin, New Zealand

The structure, functions, connections, and clinical relevance of the parvicellular and magnocellular neurons within the red nucleus have been thoroughly investigated, but the absolute number of these neurons has not. This study aimed to estimate the absolute number of parvicellular and magnocellular neurons in the red nucleus using design-based stereological counting methods and systematic random sampling techniques. Six young adult male rats, and a complete set of serial 40-µm glycolmethacrylate sections for each rat, were used to quantify neuronal numbers. After a random start, a systematic subset (i.e. every third) of the serial sections was used to estimate the total volume of the red nucleus using Cavalieri's method. The same set of sampled sections was used to estimate the number of neurons in a known subvolume (i.e. the numerical density Nv) by the optical disector method. Multiplication of the total volume by Nv yielded the absolute number of neurons. It was found that the right red nucleus consisted, on average, of 8,400 parvicellular neurons (with a coefficient of variation of 0.16) and 7,000 magnocellular neurons (0.12). These total neuronal numbers provide important data for the transfer of information through these nuclei and for species comparisons.

Poster 5.25

A comparison of the characteristics of delay neurons in the entopallium and nidopallium caudolaterale of pigeons (*Columba livia*)

M. JOHNSTON, C. ANDERSON, and M. COLOMBO
Department of Psychology, University of Otago, Dunedin, New Zealand

Working memory in humans is a type of short-term memory in which information can be processed and manipulated in order to solve a current task. Nonhuman animals also display all the characteristics of working memory and are often used to study its neural basis. We recorded single-unit neuronal activity from the nidopallium caudolaterale, the avian equivalent of mammalian prefrontal cortex, and the entopallium, the avian equivalent of the mammalian visual cortex, in four birds trained on a differential outcomes delayed matching-tosample procedure in which a skateboard sample stimulus was followed by reward and a flower sample stimulus was not. The prevailing view is that the sustained activation during the delay period reflects a neural correlate of the animal remembering information that can be used to complete the task successfully. We found that in entopallium delay activity occurred following both rewarded and non-rewarded stimuli. In nidopallium caudolaterale, on the other hand, delay activity tended to occur following the rewarded stimulus but not the non-rewarded stimulus. These findings are in line with the view that delay activity in entopallium represents a code of the sample stimulus whereas delay activity in nidopallium caudolaterale represents a code of the possibility of an upcoming reward However, we argue that although both areas support the retention of information, the activity in each area is differentially modulated by external factors.

Poster 5.26

Exploring the temporal development of sensory suppression using the N170

O. SALTMARSH, S. VOGETI, and P. M. CORBALLIS
School of Psychology, University of Auckland, Auckland, New Zealand

When two or more faces are presented at the same time, they appear to 'compete' for representation in the visual system (Desimone & Duncan, 1995). Evidence for this comes from several studies investigating the modulation of the N170 component of the event-related potential (ERP) when a stimulus is presented (e.g., Jacques & Rossion, 2006). The N170 evoked by the presentation of a target face is attenuated in amplitude when the face is flanked by other faces compared to when it is flanked by other objects or by phase-scrambled faces. Similarly, the N170 evoked by a target face is reduced in amplitude when another face is presented prior to it. This is referred to as adaptation, or repetition suppression (Grill-Spector, Henson, Martin, 2006). It has recently been suggested that both competition and adaptation may reflect a stage of the same underlying process (Kovacs, Zimmer, Volverg, Lavric, & Rossion, 2013). In the present experiment, we aim to examine the temporal development of competition and adaptation by examining the amplitude of the N170 evoked for target stimuli using both paradigms with the same participants. Here we presented i) a single target, ii) a target and two peripheral flankers simultaneously, iii) two peripheral flankers followed by a target (as in competition paradigms), and iv) a central image followed by the target (as in adaptation paradigms). We found a significantly greater reduction in the N170 amplitude for target faces versus phase scrambled controls in the fourth (adaptation) condition compared with the third (competition) condition. In addition, the N170 evoked by simultaneously presented stimuli was greater for faces than phase-scrambled controls. In contrast to previous accounts, these preliminary results suggest that the N170 attenuation observed during competition and adaptation paradigms may reflect different underlying neural mechanisms.

Poster 5.27

Age- and gender-specific changes of the GABAA receptor signaling components in the human entorhinal cortex

S. C. DODD, A. KWAKOWSKY, H. J. WALDVOGEL, and R. L. M. FAULL

Department of Anatomy and Medical Imaging, Centre for Brain Research, University of Auckland, Auckland, New Zealand

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the nervous system. GABAA receptors (GABAARs) are perhaps the most important aspect of the GABAergic signaling system for diversity of function. Variation in function of different GABAARs can be attributed to the range of subunits that forming GABAARs. Subunit composition changes over the lifetime and is implicated in not only normal aging, but also the pathology of several diseases. The entorhinal cortex (ECx) is one of the most important memory centers, primarily functioning to relay messages to and from the hippocampus. It is impaired during aging and age-related disorders. We hypothesise that alteration in subunit composition will change the function of GABAergic channels, thereby affecting GABAergic inhibition in the ECx through aging. Furthermore, gender differences may also contribute to subunit diversity. This study is the first detailed analysis of the age- and gender-specific changes of the GABA signalling components (synthesising enzymes, receptors and transporters) in the human ECx using Western blotting and confocal microscopy. Our results show a significant increase in GABAAR beta 3 subunit protein expression with age in male but not female ECx. γ2 subunit expression shows increase with age in males but not females and older females express more γ2 protein than males. However, the GABAAR alpha1 subunits did not show significant differences between age and gender groups. In conclusion, GABAAR subunit composition changes might influence GABAAR function through normal aging and affect GABAergic inhibition within the ECx.

Poster 5.28

Lipidome changes in the human caudate nucleus in Huntington's disease

M. GHODRATIPOUR, A. GREY, R. L. M FAULL, and M. A. CURTIS

Centre for Brain Research, University of Auckland, Auckland, New Zealand

The brain is replete in lipids and homoeostasis of these molecules is essential for CNS function. Lipid aberrations including endocannabinoids and cholesterol have been observed in Huntington's disease (HD). However, little is known about the distribution or abundance of a wider range of lipids. Here we used matrix-assisted laser desorption/ionisation imaging mass spectrometry to characterise global changes in the abundance and spatial distribution of lipids in 10 normal and 13 HD human caudate nuclei (CN) that were age-, and post-mortem delay matched. Pre-processing, peak finding and calibration of spectral data were performed in flexAnalysis. Relative abundance and spatial distribution of ionised lipids were analysed in SCiLS Lab. Grey matter, defined by hierarchical clustering and confirmed by H&E post-staining, was the focus of statistical analysis of lipid differences. Multivariate statistics revealed sources of variance within data. Receiver operating characteristics and one-sample *t*-tests identified lipids with significantly altered abundance in HD. Peak assignments were made using LC-MS/MS and the LIPIDMAPS database. In positive and negative polarity, 256 and 331 mass signals were detected, respectively. Principal component analysis discriminated HD and control cases, indicating distinct lipidomes. While the majority of lipids were unchanged in HD, tentative assignments suggested HD CN have less of the antioxidant α-tocopherol and the neuroprotective fatty acid docosahexaenoate. HD CN also had lower levels of several ceramides, with higher levels of corresponding ceramide-1-phosphates. A rheostatic switch toward ceramide phosphorylation is consistent with known striatal localisation of microglia in HD and may have implications in neuroinflammation and excitotoxicity in HD.

Poster 5.29

Differentiation, innervation and physiology of pluripotent stem cell-derived auditory neurons *in vitro*

M. NICHOLSON[1], N. GUNEWARDENE[2], M. DOTTORI[3], R. T. RICHARDSON[1], K. NEEDHAM[4], and B. A. NAYAGAM[1,5]

[1]Bionics Institute, Melbourne, Australia, [2]Eaton-Peabody Laboratory for Auditory Physiology, Harvard Medical School, Boston, United States of America

[3]Centre for Neural Engineering, [4]Department of Otolaryngology,[5]Department of Audiology and Speech Pathology, University of Melbourne, Melbourne, Australia

This project examined the directed differentiation of several human pluripotent stem cell types into bipolar, sensory, auditory-like neurons with biochemical, electrophysiological and synapse-forming properties that would make them suitable for a neural cell replacement therapy for hearing loss. Our published induction protocol was used to differentiate two human induced pluripotent stem cell (hiPSC) lines and one human pluripotent stem cell (hPSC) line towards a neurosensory lineage *in vitro*. Immunocytochemistry and qPCR were used to examine the expression of a cohort of relevant auditory neural markers at defined time points of differentiation. Whole-cell patch-clamp electrophysiology was used to determine whether stem cell-derived neurons were functional. Stem cell-derived neurons were then co-cultured with cochlear hair cell explants up to two weeks *in vitro*, to determine their ability to make new synapses on appropriate tissues. Both hiPSCs- and hPSCs-derived neurons expressed a cohort of relevant lineage markers including *Pax7*, *Pax2*, *Sox2*, *NeuroD1*, *Islet1*, *Brn3a*, *GATA3*, Neurofilament 160kDa, ßIII-tubulin, Peripherin and VGLUT1. All stem cell-derived neurons were similarly electrically active over 5 weeks *in vitro*. In explant co-cultures, both hiPSC- and hPSC-derived neurons made widespread synapses on inner and outer hair cells with varying degrees of efficiency (hESC>IPS2>IPS1). In future, stem cell-derived neurons could be used in combination with gene therapies such as Atoh1, to target and synapse with newly regenerating hair cells.

Poster 5.30

Zinc and NMDAR dependent changes in excitatory glutamatergic synapses expressing autism spectrum disorder associated Shank2 mutations

Y. VYAS[1], C. C. GARNER[2], and J. M. MONTGOMERY[1]

[1]Centre for Brain Research, Department of Physiology, University of Auckland, Auckland, New Zealand

[2]German Center for Neurodegenerative Diseases, Charité - Universitätsmedizin Berlin, Germany

Autism Spectrum Disorders (ASDs) are neurodevelopmental disorders characterised by deficits in social communication and interactions, and repetitive behaviours. ASDs have a strong genetic basis with mutations involved in the development and function of neural circuitry. Shank proteins act as master regulators of excitatory glutamatergic synapses and Shank mutations have been found in ASD patients. Here we have investigated the impact of ASD-associated Shank2 mutations at the synaptic level. Dissociated rat hippocampal cultures were transfected with plasmid control (EGFP-C1), EGFP-Shank2-Wildtype (WT), and Shank2 point mutations (EGFP-Shank2-S557N, -V717F, -D1535N and -L1722P). In comparison to Shank2 WT, ASD-associated Shank2 mutations induced significant decreases in synaptic density (p-value<0.05) in hippocampal neurons. Analysis of glutamate receptor expression revealed reductions in the density of NMDA receptor expressing synapses and blocking NMDA receptors caused further reductions in synapse density. These ASD-associated synaptic deficits accompanied with reduced surface receptor levels may have adverse consequences on synapse function and the overall hippocampal circuitry. Chronic application of zinc, a commonly found mineral in the brain that directly binds to Shank2, prevented the development of synaptic deficits in these Shank2 mutated neurons. However, zinc was unable to rescue synaptic deficits when NMDA receptors were chronically blocked. This demonstrates that functional NMDA receptors are necessary for the zinc-induced rescue in synapse density observed in ASD-associated Shank2 mutations. These experiments begin to decipher the mechanism underlying the observed zinc-effect. Understanding these pathways may prove key to treating the intellectual disabilities and behavioural deficits characteristic of ASDs.

Poster 5.31

In vivo monitoring of viral mediated gene injection therapy in ovine Batten disease

K. N. RUSSELL, N. L. MITCHELL, M. P. WELLBY, G. K. BARRELL, and D.N. PALMER
Faculty of Agriculture and Life Sciences, Lincoln University, Lincoln, New Zealand

Batten disease (neuronal ceroid-lipofuscinoses, NCLs) is a group of fatal brain wasting diseases of children caused by mutations in at least 13 genes. Forms associated with mutations in two different genes, *CLN5* and *CLN6*, are being investigated in well-established sheep models. Defining features are progressive atrophy of the brain and retina, leading to mental degeneration and blindness. Previous and on-going viral mediated gene therapy trials have shown remarkable efficacy. Long term ongoing *in vivo* assessments of brain atrophy and visual impairment are essential to monitor treatment trials and provide data for possible translation to human therapies. The blindness has central and peripheral components, with both the visual cortex and retina affected and, thus, it is important to monitor each separately. Observation of the sheep in the field and maze testing showed a relatively early visual impairment that correlates with the onset of atrophy of the visual cortex (around 6 months of age), whereas electroretinography (ERG) showed that retinal degeneration occurred later and developed more slowly. The amplitudes of both a- and b-waves were significantly reduced at 7 and 9 months respectively in CLN5-/- sheep ($p < 0.05$). CLN6 -/- sheep had a later onset of retinal blindness. Computed tomography (CT) imaging revealed a longitudinal reduction of intracranial volume and increased volumes of the lateral and third cerebral ventricles in NCL affected sheep compared with unaffected controls. These changes can be modelled from CT scans using 3-D software and accurate models can be built for CT guided stereotactic injection of viral mediated gene therapy.

Poster 5.32

Quantification of new synapses by stem cell-derived neurons on developing peripheral and central auditory tissues *in vitro*

T. HYAKUMURA[1,2], M. DOTTORI[3], and B.A. NAYAGAM[1,2]
[1]*Bionics Institute, Melbourne, Australia*
[2]*Department of Audiology and Speech Pathology,* [3]*Centre for Neural Engineering, University of Melbourne, Melbourne, Australia*

The loss of auditory neurons that occurs with profound hearing loss is irreversible in humans. Stem cell therapy for auditory neuron replacement thereby offers potential for hearing restoration in patients with profound deafness. This project aimed to investigate and quantify the formation of new synapses between human pluripotent stem cell (hPSC)-derived neurons and target peripheral and central auditory tissues *in vitro*, including an *in vivo* comparison with developing synapses in the mammalian auditory system. Sensory neurons were generated from hPSCs over 21 days *in vitro* and then co-cultured with sensory hair cell explants (n=60) and cochlear nucleus slices (n=12) for a further 2 weeks. Synaptogenesis in the developing mammalian cochlea and cochlear nucleus was also examined over a time-course spanning from birth through to adulthood, for comparison. Synapse formation was examined using four-channel immunofluorescence and confocal microscopy and analysed using ImageJ software. Stem cell-derived neurons expressed synapsin 1 and vesicular glutamate transporter-1 at sites of innervation with both hair cells and cochlear nucleus neurons. This observation is consistent with results from control cocultures of auditory neurons with either hair cell explants or cochlear nucleus slice. Significantly more synaptic contacts were observed in stem cell cocultures in comparison to controls ($P \leq 0.05$). Moreover, new synapses from stem cell-derived neurons *in vitro* corresponded anatomically with early synaptogenesis in the developing mammalian auditory system. This assay describes the characterisation, timing and quantification of new synaptic connections by stem cell-derived neurons *in vitro*. Correct synapse formation is an essential component in the development of a stem cell therapy for profound hearing loss.

Poster 5.33

Analgesic and anti-inflammatory effects of novel kappa opioid receptor agonists

K. F. PATON[1], T. E. PRISINZANO[2], and B. M. KIVELL[1]

[1]*Centre for Biodiscovery, Victoria University of Wellington, Wellington, New Zealand*

[2]*Department of Medicinal Chemistry, University of Kansas, Kansas, United States of America*

Pain management is a worldwide problem and is still the most common reason for visiting the doctor, creating a large economic burden. Analgesic drugs activating the mu-opioid receptor are used routinely to treat severe acute and chronic pain, however, side effects include nausea, constipation, respiratory depression, addiction and long-term use leads to tolerance. In contrast, kappa opioid receptor (KOPr) agonists, such as the naturally-occurring Salvinorin A (SalA), have analgesic properties with little potential for abuse. We have studied two novel analogues of SalA, 16-ethynyl SalA and 16-bromo SalA in preclinical models of pain and inflammation. Intraperitoneal administration of 16-ethynyl SalA and 16-bromo SalA at 2 mg/kg in the formalin (2%) footpad model decreased both nociceptive and inflammatory pain and also caused a decrease in footpad oedema compared to vehicle/formalin treated mice. The KOPr antagonist nor-binaltorphimine (10 mg/kg) reversed the analgesic effect of the novel compounds. The tail withdrawal assay was used to measure the centrally-mediated analgesic properties, both 16-ethynyl and 16-bromo SalA showed a longer duration of action with an analgesic effect up to 60 min, when compared to the parent compound SalA which was active up to 30 min. Motor incoordination was measured with the rotarod performance test, with 16-bromo SalA showing a significant decrease in impairment compared to the sedative effects of morphine (10 mg/kg), whilst 16-ethynyl SalA showed impairment for 30min at 1 and 2 mg/kg. This study demonstrates the potential for KOPr agonists for the treatment of acute pain and inflammation.

Poster 5.34

Rapid effects of neurosteroids DHEA, 7α-OH-DHEA and 7β-OH-DHEA on the ACh-induced calcium-influx in honeybee (*Apis mellifera*) kenyon cells

A. LOEHFELM[1,2], A. TUPS[2], and U. MUELLER[1]

[1]*Biosciences Zoology/Physiology-Neurobiology, Saarland University, Saarbruecken, Germany*

[2]*Centre for Neuroendocrinology and Brain Health Research Centre, Department of Physiology, University of Otago, Dunedin, New Zealand*

Neuroactive steroid hormones or neurosteroids with neuroprotective effects became more and more interesting in the last years due to their implication in aging and age-related neurodegenerative diseases like Alzheimer's and Parkinson's disease. The term neurosteroid was formed for neuroactive compounds produced *de novo* in the brain and for circulating steroids metabolized in the CNS to neuroactive forms. Although it is known that neurosteroids modulate ion-gated neurotransmitter receptors as $GABA_A$ or NMDA receptors, acetylcholine receptors were not yet studied intensively regarding neuroprotection. Using optical imaging in primary honeybee Kenyon cells this work aimed to characterize immediate effects of the neurosteroids DHEA, 7α-OH-DHEA and 7β-OH-DHEA on calcium influx triggered by acetylcholine receptors. Thus, it was shown for the first time that the neurosteroids are able to alter the ACh-induced calcium stream in a time-dependent and stereospecific manner. These results furthermore indicate that different kinases, phosphatases and the release of intracellular calcium from the endoplasmic reticulum (ER) are involved in the modulation of the nACh receptor types' sensitivities.

Poster 5.35

Electrophysiological coherence across anterior thalamic, hippocampal and prefrontal cortex during anaesthesia after mammillothalamic tract lesions

S. C. BARNETT[1,3], B. A. L. PERRY[1,3], J. LEE[1], J. J. HAMILTON[1,3], N. McNAUGHTON[4], and J. C. DALRYMPLE-ALFORD[1,2,3]

[1]Department of Psychology, University of Canterbury, Christchurch, New Zealand
[2]New Zealand Brain Research Institute, Christchurch, New Zealand
[3]Brain Research New Zealand, Universities of Auckland and Otago
[4]Department of Psychology, University of Otago, Dunedin, New Zealand

Episodic memory depends on a distributed circuit of neural structures, known as the extended hippocampal system. Damage to the mammillothalamic tract (MTT) is associated with clinically severe memory deficits. The MTT provides a unique afferent pathway to the anterior thalamic nuclei (ATN) from the mammillary bodies. We examined the influence of MTT lesions in rats on the electrophysiological coherence (viewed as evidence of communication between structures) of neural rhythmic activity between key memory structures during isoflurane anaesthesia. For baseline recordings (2s epochs over 60s), MTT rats showed significantly weaker coherence than SHAM rats in beta frequencies (13-30 Hz) among the ATN, prefrontal cortex (PFC) and dorsal hippocampus (HPC), with the greatest deficit for ATN:HPC (effect size, d= .71). MTT lesions also decreased delta (1-4 Hz) frequency HPC:ATN coherence (d= .94) and theta (4-7 Hz) frequency PFC:ATN coherence (d=.63). No differences were found in alpha (8-12 Hz) or gamma frequency (30-100 Hz) coherences. One minute after the cessation of one minute of 100Hz stimulation of the ATN, beta frequency coherence in SHAM rats was reduced to that shown by MTT rats, but delta and theta coherences were unaffected. These results show that MTT lesions impair electrophysiological coherence across the extended hippocampal system and in a similar way to the effect of 100Hz stimulation of the ATN on beta frequency coherence. Changes to functional communication among key memory structures may be causally related to memory impairments associated with MTT lesions.

Poster 5.36

Competition for representation between everyday object categories as a tool to explore the functional architecture of the visual system

G. R. PATEL and P. M. CORBALLIS

School of Psychology, University of Auckland, Auckland, New Zealand

Competition for representation between objects in the ventral visual stream has the potential to reveal information about the functional architecture of the visual cortex. The N1 component of the event-related potential (ERP) is attenuated when an object is presented in the context of another object from the same category, reflecting shared neural resources and competition for representation, whereas no competition is observed between distinct object categories. This has been established with specialised categories, such as faces, but has yet to be confirmed as a more general effect. We aimed to establish this within- but not between-category competition for more general object categories, but more importantly to explore the nature of competition. A flanker task was used to present target images from the object category of sedan cars in the context of either other vehicles (sedans, motorbikes, trucks, SUVs), pianos, or phase-scrambled images. Neural activity was measured using EEG. Preliminary results suggest within-category competition, manifested as N1 attenuation, in the sedan-flanker condition, but no evidence of between-category competition, with N1 amplitudes observed in the piano-flanker condition similar to those in the phase-scrambled-flanker condition. Most interestingly, there is evidence of graded competition, with vehicle subcategory flankers showing competition for representation, but at an intermediate level. These results suggest that the degree of competition reflects the degree of shared resources between two objects presented, and supports categorical organisation of processing pathways in the visual system. This study provides a base for future research to investigate the nature of these pathways and the features that result in competitive interactions.

Poster 5.37

The role of saturated and unsaturated fatty acids in neuro-inflammation and insulin sensitivity in a hypothalamic cell culture system

K. KAMSTRA[1], M. BENZLER[2], and A. TUPS[1,2]

[1]*Centre for Neuroendocrinology, Brain Health Research Centre, Department of Physiology, University of Otago, Dunedin, New Zealand*

[2]*Department of Animal Physiology, Philipps University Marburg, Marburg, Germany*

Overnutrition is the major cause for the development of metabolic diseases, such as obesity and type 2 diabetes. There is strong evidence that increased circulating levels of saturated free fatty acids (sFFAs) in the brain are involved in the induction of hypothalamic neuro-inflammation, thereby leading to disturbed energy homeostasis and central insulin resistance. In contrast to sFFAs, polyunsaturated n-3 fatty acids (PUFAs) seem to prevent from sFFA-induced inflammation and insulin resistance. However, the exact underlying molecular mechanisms how sFFAs are able to induce neuro-inflammation and how this is counteracted by PUFAs are still under debate. Therefore, we investigated the effect of the sFFA Palmitic acid (PA) and the PUFA Docosahexaenoic acid (DHA) in a hypothalamic cell culture system. To that end, adult hypothalamic mouse cells (mHypoA-2/30 (CEDARLANE® CELLusions BIOSYSTEMS)) were treated with either 200 µM PA or 200 µM DHA or with a combination of both fatty acids for different time periods in the presence or absence of 10 nM Insulin (Ins). We found a time-dependent effect of PA on inflammation, as measured by western blot analysis of phosphorylated NFkB-p65. Interestingly, this effect was counteracted by DA and moreover, also influences levels of phosphorylated Akt, a marker of insulin sensitivity. This study reveals opposing effects of saturated versus unsaturated fatty acids on neuro-inflammation and insulin sensitivity.

Poster 5.38

An evaluation of language in brain tumour patients using a new cognitively-motivated testing protocol

C. WILSHIRE[1] J. FAULKNER[1], A. PARKER[2], and K. CUNNINGHAM[1]

[1]*School of Psychology, Victoria University of Wellington, Wellington, New Zealand*

[2]*Wellington Hospital, Wellington, New Zealand*

One important goal in the treatment and management of neurological tumours is the maximization of language function. This goal cannot be achieved unless we have effective and sensitive methods of assessing language function in this population. This study aimed to characterise the language impairments that occur in brain tumour patients both pre- and postoperatively using a new assessment that draws on recent cognitive neuropsychological models of language function. An undifferentiated sample of 53 patients with cerebral tumours admitted to hospital for neurosurgery completed a new testing protocol, the BLAST. This protocol assesses eight well documented, "core" cognitive skills required for language: auditory word recognition, accessing semantic knowledge, lexical selection, phonological encoding, verbal short term memory, goal-driven response selection, verb retrieval, and articulatory-motor planning. Patients were unselected with respect to lesion location. A surprising 53% of patients scored below controls on at least one core skill. Group based analysis and voxel-based lesion-symptom mapping methods revealed that preoperatively, left temporal tumours were associated with deficits to the following skills: phonological encoding, lexical selection, accessing semantic knowledge and verbal short-term memory. Left frontal tumours were associated with deficits involving articulatory-motor planning and goal-driven response selection. These findings are consistent with studies examining the anatomical substrates of our "core" cognitive processes in other populations. We conclude that selective impairments in key language skills are common in brain tumour patients, but many of these are not adequately assessed on conventional aphasia assessments. Our protocol may provide a useful resource for preoperative, postoperative and intraoperative language assessment in this population.

Poster 5.39

Calcium dynamics in coupled cellular reaction diffusion equations

M. L. GOODMAN[1,2], T. DAVID[1,2], P. D. DOCHERTY[1], and R. MURRAY[3]
[1]Department of Mechanical Engineering, [2]University of Canterbury High Performance Computing, [3]Department of Mathematics and Statistics, University of Canterbury, Christchurch, New Zealand

Vasomotion of the cerebral arteries has been identified as a possible bio-marker for Alzheimer's disease (AD). Recent experiments by our colleague in Sheffield (Dr John Berwick) seem to indicate that vasomotion could be more prevalent in those suffering from AD. Waves of cytosolic calcium concentration, mediated by connexion gap junctions, can provide the co-ordinated environment for vasomotion. Calcium concentration across a coupled cell was modelled using a homogenised implementation of the Goldbeter *et al.* (1990) model. Cells were coupled spatially with a gradient of the stimulus (β) from the neuron and with either linear Fickian or Electro Diffusion. High and low β levels produced constant calcium concentration in the cytosol whilst intermediary β produced oscillations. The outcomes were compared to simplified 'Toy-models' with sinusoidal inputs. The coupled Goldbeter model yielded interesting wave shapes with waves propagating into regions where zero-diffusion implies oscillations should not exist. There were minimal differences in behaviour across Electro and Fickian diffusion. In contrast, one of the Toy models yielded no such wave propagation due to the wave shape and frequency. We have determined that the shape of the cell's calcium concentration profile influences the depth of wave propagation into the non-oscillatory region. In particular, waves with cnoidal tendencies lead to wave propagation, whereas sinusoidal waves do not. This insight leads to an improved understanding of how vasomotion interacts with normal perfusion in the cortex that may be a bio-marker for AD.

Poster 5.40

Breaking of Kanizsa figure completion evokes a behavior-free signal of perceptual prediction error

M. OXNER, S. McGILL, W. G. HAYWARD, and P. M. CORBALLIS
School of Psychology, University of Auckland, Auckland, New Zealand

Perception as an inferential and predictive process has been a recurring theme since von Helmholtz. For example, the illusory contours of the Kanizsa figure are thought to result from a perceptual inference of unseen, occluding objects. Although the neural correlates of perceptual completion have been described before, little is known about how conflicting sensory evidence interacts with this ongoing "perceptual hypothesis". Here, we investigated the event-related potentials (ERPs) of a perceptual prediction error, evoked when perceptual completion is broken by subsequent, inconsistent motion. Eleven participants performed an unrelated probe detection task while electrical scalp activity was recorded using EEG; simultaneously, task-irrelevant arrays of four inducers ("pacmen") were presented which either formed a Kanizsa square or were perceptually incomplete. After one second of static presentation, inducers rotated dynamically so as to either support the hypothesis of an occluding surface (completion-preserving) or disconfirm this percept (completion-breaking). Consistent with previous work (e.g. Murray, Foxe, Javitt, & Foxe, 2004), the initial static presentation of completed Kanizsa squares evoked more negativity than incomplete inducer arrays in lateral occipital electrodes, in the N1 component and between 250 and 350ms following static presentation. In the dynamic phase, a negative wave passed from central to occipitoparietal electrodes between 100 and 200ms after motion onset for completion-breaking (i.e. hypothesis-violating) inducer motion when compared to completion-preserving motion. To our knowledge, this violation-related signal is the first demonstration of a correlate of perceptual prediction error that is independent of task, salience, and stimulus contingencies. Its scalp distribution implies the involvement of high-level regions of the cortical visual hierarchy in the reassessment of perceptual hypotheses and the perception of illusory contours.

Poster 5.41

Age- and gender-specific changes of the GABAA receptor signalling components in the human inferior-, middle- and superior temporal gyrus

M. PANDYA, H. J. WALDVOGEL, R. L. M. FAULL, and A. KWAKOWSKY
Department of Anatomy and Medical Imaging and Centre for Brain Research, University of Auckland, Auckland, New Zealand

Gamma Aminobutyric Acid (GABA) is the chief inhibitory neurotransmitter in mammalian central nervous system. GABA A receptors (GABAAR) are pentameric ionotropic channels formed via amalgamation of subunits (>20 isoforms). Subunit composition of receptors is associated with the affinity of GABA binding and its downstream inhibitory actions. Fluctuations in subunit expression levels throughout stages of life has been demonstrated in animal studies at the RNA and protein level. Similarly, human studies showed age-related subunit changes, which are exaggerated in diseased states such as Alzheimer's disease. Also, a few studies reported that hormonal changes have implications on the GABAAR signalling system suggesting gender-related changes in GABAAR subunit composition. However, our knowledge is highly based on animal models and with controversial findings. Our study is the first to investigate the age- and gender-related changes of the GABAAR subunit expression in the human superior-, middle- and inferior temporal gyrus. Examination was conducted on: 6 young females (~49.8 years), 6 young males (~ 47.5 years), 6 elderly females (~ 75.7 years) and 6 elderly males (~79 years) using Western blotting and Immunohistochemistry. We observed a significant gender-dependent difference in GABAAR alpha1 subunit expression; males presenting significantly higher levels compared to woman across all stages of life in superior temporal gyrus. No significant age- or gender-related differences were found in alpha5, beta3 and gamma2 GABAAR subunit expression. In summary, gender-related GABAAR subunit composition changes might influence GABAAR function and affect GABAergic inhibition. Furthermore, GABAARs are well preserved during normal aging in the human superior-, middle- and inferior temporal gyrus.

Poster 5.42

Post-weight loss changes in brain activity after a very low calorie diet

S. ROSS[1], P. MANNING[1], D. DeRIDDER[2], W. SUTHERLAND[1], S. LEONG[2], A. RYALLS[1], A. ANDERSON[1], E. BERRY[1], G. HENDRY[1], S. VANNESTE[4], and C. HORWATH[3]
[1]Department of Medicine, [2]Department of Surgical Sciences, [3]Department of Human Nutrition, University of Otago, Dunedin, New Zealand
[4]School of Behavioural and Brain Sciences, University Of Texas at Dallas, Dallas, United States of America

Weight loss in obese individuals has known impacts on brain activity that can increase the drive to eat and lead to weight regain. Understanding these changes may help to influence weight loss or prevention of weight regain strategies to increase success and alleviate some obesity associated symptoms. The POWER study is a Prevention Of WEight Regain study in which obese subjects (BMI≤30) undertake 4 weeks of a very low calorie diet (Optifast) in order to lose 5%+ of their body weight. A subset of these subjects were recruited for brain imaging study using electroencephalogram (EEG) imaging to identify fasting brain activity changes before and after weight loss. Other appetite measures such as gut hormones and self-reported appetite were also investigated. This study revealed that weight loss of 5%+ body weight lead to changes in areas of the brain associated with hunger processing and inhibitory control. This was reflected in self-reported appetite measures and gut hormones and indicated that participants were hungrier and had a reduction in inhibitory control related to the amount of weight lost. This supports current literature and also provides specific brain regions that can be targeted to increase success with weight loss therapies either with behavioural or neurostimulatory procedures.

Poster 5.43

A clinically authentic murine model of acute brainstem encephalitis and neurogenic pulmonary edema induced by Enterovirus 71

V. T. K. CHOW[1], C. B. VICTORIO[1,2], Y. XU1[2], Q. NG[2], B. H. CHUA[3], S. ALONSO[1], and K. B. CHUA[2]

[1]Department of Microbiology and Immunology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

[2]Temasek Lifesciences Laboratory, Singapore

[3]Office of Research and Development, Curtin University, Perth, Australia

Enterovirus 71 (EV71) is a neurotropic virus that sporadically causes fatal neurologic illness among some infected children. We have established a mouse model of EV71 infection displaying neurogenic pulmonary edema (NPE) in severely affected animals. We inoculated one-week-old BALB/c mice with a mouse-adapted EV71 strain, and identified clinical signs consistent with observations in human cases and other animal models. Respiratory distress was also evident in certain mice. At necropsy, their lungs were heavier and incompletely collapsed compared to other mice. Serum levels of catecholamines and histopathology of lung and brain tissues of these mice strongly indicated features of NPE. The localization of virally-induced brain lesions also suggested a potential pathogenic mechanism for EV71-induced NPE. We propose that acute, severe destruction of brainstem tissue leads to a cathecolamine storm that progresses to NPE if trigger zones in the brainstem become sufficiently damaged by the virus. This novel murine model of virally-induced NPE represents a valuable resource for studying viral mechanisms of neuro-pathogenesis, and for pre-clinical testing of potential therapeutics and prophylactics against EV71-related neurologic complications.

Poster 5.44

A neurophysiological and behavioural assessment of interventions targeting attention bias and self-control in binge drinking

J. E. LANGBRIDGE[1,2], J. J. CANALES[1,3], and R. D. JONES[1,2]

[1]Department of Psychology, University of Canterbury, Christchurch, New Zealand

[2]New Zealand Brain Research Institute, Christchurch, New Zealand

[3]Department of Neuroscience, Psychology and Behaviour, University of Leicester, Leicester, United Kingdom

Attention bias modification (ABM) can decrease the selective visual attention paid to alcohol-related cues, but has not been found to reliably reduce alcohol craving. Here, an intervention to decrease craving by increasing sense of control (Shamloo & Cox, 2014) was proposed as a complement. We investigated the effects of two such brief interventions administered singly or in combination. The combination was hypothesised to be more effective than either intervention alone. Participants were 41 binge drinkers (BDs) and 10 non-binge drinkers (NBDs), defined with a binge score measure. BDs received either ABM, sense of control training, both interventions, or no intervention, and were compared with NBDs who received no intervention. Groups were assessed on alcohol attention bias change, including both reaction times and cue-elicited ERPs in a visual dot-probe task, alcohol craving change, and alcohol consumption. BDs showed a non-significant trend for higher attention bias scores than NBDs. ABM had no effect on BDs' behavioural or electrophysiological markers of attention bias. Sense of control training did not increase personal sense of control, failing to replicate previous reports, but did seem to protect against decreased task accuracy and against increased craving. BDs receiving the combined intervention consumed less alcohol in a bogus taste test than participants receiving no intervention. Taken together, the results do not lend support for ABM as an effective intervention but suggest that ABM may reduce alcohol consumption if combined with sense of control training.

Poster 5.45

A "core skills" approach to the assessment of acquired language disorders

V. E. LEE, C. E. WILSHIRE, and J. W. FAULKNER
School of Psychology, Victoria University of Wellington, Wellington, New Zealand

The majority of diagnostic assessments of *aphasia* are based upon the classical model of language. A major limitation of these diagnostic assessments is that they are based upon a very simple neuroanatomical model of language function. In the decades since the classical model, cognitive theories of language function have developed considerably, which provides a much richer framework for the assessment of acquired language disorders. On the basis of this framework, Faulkner, Wilshire, Parker, and Cunningham (2015) developed the *Brief Language Assessment for Surgical Tumours* (*BLAST*) for the assessment of language function in brain tumour patients. In the current study, we evaluate the efficacy of the BLAST in individuals with chronic post-stroke aphasia, cross-validate the core cognitive skills identified by the BLAST with independent measures argued to index the same theoretical construct, and evaluate whether an individual's linguistic profile on the BLAST is predictive of performance on a more naturalistic sentence production task. The results from the current research can be divided into three primary findings. First, we found that the BLAST could be administered to individuals with post-stroke aphasia, and that the linguistic profiles provided by the BLAST extend far beyond the predictions derived from neural localization and classical diagnostic assessments. Second, we found support for the validity of five of the core cognitive skills. Third, we found some support for the notion that performance on the BLAST may be predictive of performance on a more naturalistic sentence production task. In short, the current findings suggest that the BLAST holds potential as a clinical tool for the assessment of language function in a range of different neurological populations.

Poster 5.46

Receptor studies suggest two neurochemically distinct populations of neurons in the human globus allidus

B. BLACK, H. WALDVOGEL, and R. FAULL
Centre for Brain Research, University of Auckland, Auckland, New Zealand

Huntington's disease (HD) is an inherited neurodegenerative disorder, which is characterized by motor dysfunction, cognitive decline and psychiatric symptoms. Although HD affects many areas of the brain, the most affected is the basal ganglia. These deep nuclei are involved in motor, associative and limbic functions. The globus pallidus is a core component of this assembly, ultimately becoming the main output nuclei of the many circuits which traverse the basal ganglia. The objective of this study is to examine the excitatory (glutamate) and inhibitory (GABA) pathways in and out of the internal and external segments of the globus pallidus, by use of receptors and vesicular transporter markers. Post-mortem human brain tissue blocks containing the globus pallidus were selected for sectioning. The tissue sections were stained using single and multi-labelled fluorescent immunohistochemistry; targeting receptor subunits ($GABA_A$ α1 and NMDA GluN1) and transporters (VGLUT2 and VGAT). Qualitative observations were made comparing the markers, as well as some preliminary densitometric analysis on the Zeiss LSM 710 inverted confocal microscope. The results of this study has characterized glutamate receptors and how they associate with GABA receptors as well as their transporters in the normal human brain, which will be used as a baseline for comparison with Huntington's disease cases. Remarkably, preliminary studies suggest that there are distinct neuronal populations in the globus pallidus, one that receives mainly glutamatergic input and another that receives mainly GABAergic input. Therefore, these glutamatergic systems could be new pharmacological targets for treatments of motor dysfunctions in HD.

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Poster 5.47

The relationship between behavioral characteristics and urinary excretion of monoamine neurotransmitters in children with inattention, hyperactivity-impulsivity and ASD

T. YAMAMOTO[1], M. MORINAGA[1], and M. YAMASHITA[1,2]
[1]Department of Psychology, Tezukayama University, Nara, Japan
[2]Japan Society for the Promotion of Science, Tokyo, Japan

Although previous studies have reported relationships between the neurodevelopmental disorders and neuronal activity governed by three monoamine neurotransmitters (noradrenaline, dopamine, and 5-hydroxytryptamine) in patients suffering from attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), results have been inconsistent. In the present study, we classified participants with neurodevelopmental disorders into the following groups according to the ADHD-RS and AQ-10: inattention dominant type; hyperactivity-impulsivity dominant type; and ASD-dominant type. We then compared urinary excretion of the monoamine neurotransmitter metabolites 3-methoxy-4-hydroxyphenylglycol (MHPG), homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA) in these groups with a control group. Using canonical discriminant analysis, we could distinguish by two statistically significant discriminants and one meaningful tendency discriminant the three types of neurodevelopmental disorder based on excretion of these metabolites. We found the following facts: inattention shows that MHPG and 5-HIAA are high, and HVA is low. Hyperactivity-impulsivity shows that HVA is high, and MHPG is low. ASD-dominant type shows that MHPG is high, and 5-HIAA is low. These results suggest that an imbalance in activity of the three monoamine neurotransmitters is associated with specific behavioral characteristics that are symptomatic of these neurodevelopmental disorders. Further, analyzing urine samples, as in this study, may represent a useful non-invasive method of examining brain monoamine dynamics.

Poster 5.48

Epigenetic markers in the extended hippocampal memory system after diencephalic lesions

F. D. DOAKE[1], S. C. BARNETT[1], B. A. L. PERRY[1], S. A. MERCER[4], and J. C. DALRYMPLE-ALFORD[1,2,3]
[1]Department of Psychology, University of Canterbury, Christchurch New Zealand
[2]New Zealand Brain Research Institute, Christchurch, New Zealand
[3]Brain Research New Zealand, Universities of Auckland and Otago, New Zealand
[4]Department of Psychology, University of Otago, Dunedin, New Zealand

Evidence from both human and animal models has consistently shown that the anterior thalamic nuclei (ATN) and mammillothalamic tract (MTT) are both key components of a distributed network of structures that support memory as part of an extended hippocampal circuit. Lesions to both the ATN and MTT in rats reliably reduce immediate early gene (IEG) activity in cortical regions of this system, most especially in the retrosplenial cortex (RSP). These IEG changes are thought to contribute to the spatial memory deficits produced by these diencephalic lesions. To explore the underlying genetic mechanisms of these effects, we used immunohistochemistry to compare H3 histone acetylation, a key epigenetic marker, and IEG activation using zif268, in subregions of the hippocampus and RSP following ATN and MTT lesions in rats. While zif268 activity was substantially reduced by both ATN and MTT lesions across the RSP and area CA1 of the dorsal hippocampus, no reliable changes were found in H3 expression after either lesion. These results suggest that whilst there is a clear lesion effect on downstream IEG activation following both ATN and MTT lesions, changes in global H3 expression may not provide a genetic correlate of this cellular hypoactivity. One possible explanation for this negative finding is that H3 is non-specific epigenetic regulator of gene expression, and thus may obscure changes in specific genes related to the distal lesion effects.

Poster 5.49

Treatment of brain injury due to extreme prematurity: Effect of melatonin on ADHD-like hyperactivity

O. OKPE, L. GODDARD, and D. E. OORSCHOT
Department of Anatomy, Brain Health Research Centre, University of Otago, Dunedin, New Zealand

The birth of an extremely premature baby (≤28 weeks of gestation) is costly to health systems and involves 170-200 babies annually in New Zealand. Children born extremely prematurely can experience repeated hypoxic injury to the brain and can develop attention deficit hyperactivity disorder (ADHD). In a new rat model of repeated hypoxic brain injury during the equivalent of extreme prematurity, ADHD-like hyperactivity was observed. Yet, treatment with melatonin, which is safe in clinical neonatology and a known antagonist of the proposed biological mechanisms that generate the ADHD-like hyperactivity, has not been investigated. Hence, the aim of this study was to investigate whether treatment with melatonin prevents ADHD-like hyperactivity. Postnatal day 1-3 Sprague-Dawley male rats were exposed to repeated hypoxia and divided into treatment groups of repeated hypoxia diluent-treated (n = 9 pups) and repeated hypoxia melatonin-treated (n = 10). The rats were then behaviourally tested from 6 months-of-age on a multiple component fixed interval-extinction test. This test detects ADHD-like hyperactivity in response to delayed reward, as well as inattention. There was no significant difference between the repeated hypoxia melatonin-treated and the repeated hypoxia diluent-treated animals for ADHD-like hyperactivity (repeated measures ANOVA, $p<0.35$) or inattention (repeated measures ANOVA, $p<0.97$). This study suggests that melatonin does not prevent ADHD-like hyperactivity due to repeated hypoxic brain injury during the equivalent of extreme prematurity.

Poster 5.50

Characterisation of oxidative stress-responsive genes and gene products in ovine CLN6

J. Z. CHEN, N. L. MITCHELL, L. A. BARRY, L. F. MAO, and D. N. PALMER
Faculty of Agriculture and Life Sciences, Lincoln University, Lincoln, New Zealand

The neuronal ceroid lipofuscinoses, (NCL, Batten disease) are devastating childhood neurodegenerative diseases caused by mutations of a number of genes, but the underlying pathogenic mechanisms remain unclear. The major pathological events, including storage body accumulation, neuroinflammation and neurodegeneration are commonly thought to be associated with oxidative stress. This study investigated selected oxidative stress markers in CLN6 affected sheep brains during disease progression; mitochondrial manganese superoxide dismutase (MnSOD/SOD2), inducible nitric oxide synthase (iNOS), haem oxygenase -1 (HMOX-1) and the mitochondrial marker, cytochrome c oxidase subunit IV, (COX IV). MnSOD expression was determined by immunohistochemistry of sagittal CLN6 affected brain sections and matched controls over the span of disease development, 2, 6, 9, 18 and 24 months, n=3. Adjacent sections were immunostained for COX IV. Quantitative PCR was used to estimate the relative expressions of *MnSOD, iNOS* and *HMOX-1*. MnSOD expression throughout co-localised to mitochondria and became compressed to the boundaries between layers I and II and layers IV and V at 18 and 24 months in affected sheep, following severe neurodegeneration. There was no such compression in the non-degenerating cerebellum and brain stem. Quantification of MnSOD and COX IV across the cortical grey matter showed reduced expression at 18 months and even more at 24 months, indicating that previous reports of enhanced activity probably arose from unmatched sampling. *iNOS* was not expressed in ovine brains and HMOX-1 remained unchanged throughout the disease progression. Oxidative stress is not likely to play a role in pathogenesis and there was a species-dependent difference in inflammatory responses and cytoarchitectural changes accompanying neurodegeneration need to be considered when analysing molecular changes.

Poster 5.51

Effect of delayed post-treatment with adult-sourced adipose-derived mesenchymal stem cells on motor function and striatal medium-spiny projection neurons after neonatal rat hypoxia-ischemia

B. E. AGHOGHOVWIA, L. GODDARD, and D. E. OORSCHOT
Department of Anatomy, Brain Health Research Centre, University of Otago, Dunedin, New Zealand

Hypoxic-ischemic (HI) brain injury is a main cause of disabilities in term-born infants. This study investigated the therapeutic effects of adult-sourced adipose-derived mesenchymal stem cells (MSCs) on motor skills, and on neuronal restoration in the anterior striatum, following HI-induced brain injury. On postnatal day (PN) 7, Sprague-Dawley rat pups were exposed to HI right-sided brain injury, weight-matched and assigned to groups (n = 8-10/group) – untreated (HI+Dil), normal controls (Normal+Dil), single stem cell-treated (HI+MSCsx1) and double stem cell-treated (HI+MSCsx2). On PN14 and 16, all groups were treated with either diluent or stem cells. All animals were then tested repeatedly on the cylinder and staircase tests for their motor skill ability and perfused on PN106/107. Serial 5µm thick frozen sections were cut coronally through the brain using a cryostat and immunohistochemically stained for striatal DARPP (dopamine- and cAMP-regulated phosphoprotein-32)-positive spiny projection neurons. The absolute number of these neurons was estimated using the Cavalieri's, physical disector and Abercrombie/unfolding methods. HI groups were significantly impaired on left- versus right-sided motor skills on the staircase test (eg. HI+MSCsx1, repeated ANOVA, $p<0.005$), but the control animals were not. The absolute number of DARPP-32-positive neurons in the striatum was significantly greater (Student's t-test, $p<0.04$) in the control group compared to all HI groups. There was no statistically significant rescue of motor skills or striatal spiny projection neurons by delayed single- or double-treatment with adipose-derived MSCs. These results suggest that treatment with this particular type of stem cell has limited therapeutic potential for rescuing striatal neurons and motor deficits after neonatal hypoxia-ischemia.

Poster 5.52

Using EEG to investigate the effect of GABAergic inhibition on high frequency oscillations in the visual cortex

R. L. SUMNER[1,2], R. L. GRASS[1,2], M. D. TINGLE[1], I. J. KIRK[1,2], F. SUNDRAM[1], and S. D. MUTHUKUMARASWAMY[1,2]
[1]School of Psychology, [2]School of Pharmacy, [3]School of Psychological Medicine, [4]Department of Pharmacology and Clinical Pharmacology, [5]Centre for Brain Research, University of Auckland, Auckland, New Zealand

Advancements in the use of electroencephalography (EEG) to investigate potential biomarkers of cortical excitability may help to understand the biological basis of neurological disorders. Changes to synchronous oscillations within the gamma band can indicate imbalance of excitation/inhibition related to the inhibitory neurotransmitter GABA, as GABA dysfunction has been implicated in many central nervous system disorders. Research has shown that increases in GABAergic inhibition increase the amplitude and decrease the frequency of induced gamma oscillations. We conducted a study on the effect of the GABAergic drug lorazepam on visually induced gamma oscillations in healthy male volunteers (n=20) using EEG. Ninety minutes following administration of either the drug or placebo, participants completed a task designed specifically to generate high frequency oscillatory activity in the visual cortex. Using a linearly constrained minimum variance beamforming approach for source localisation, we found significant gains in power detection of over 100% compared to standard methods for pre-processing data including independent component analysis. However, in these data we found no difference in frequency (M_{Drug}=60Hz; $M_{Placebo}$=61Hz, p=0.57) or amplitude (M_{Drug}=76; $M_{Placebo}$=91, p=0.21) of gamma oscillations between the two conditions. Further, reproducibility metrics for gamma frequency estimation demonstrated that our estimates were highly reliable indicating that our lack of difference is not due to issues with signal-to-noise ratio. Possible reasons for the change include saturation of gamma activity by a moving stimulus or an unexpected dose-response relationship. This suggests that there is a more complex relationship between induced gamma oscillation parameters and GABA than has previously been considered.

Poster 5.53

Regional changes in mouse motor cortex excitability after focal stroke

E. M. POWER[1], E. K. GOWING[2], A. N. CLARKSON[2,3], and R. M. EMPSON[1]
[1]Department of Physiology, [2]Department of Anatomy, Brain Health Research Centre, Brain Research New Zealand, University of Otago, Dunedin, New Zealand
[3]Faculty of Pharmacy, University of Sydney, Sydney, Australia

About 9000 people in New Zealand have a stroke every year (Stroke.org.nz). It is the third leading cause of mortality and, for those who survive, it can cause a range of permanent disabilities. In this project we aimed to understand changes in functional connectivity in the motor cortex after stroke in order to identify mechanisms that can influence recovery. Here, we use a transgenic mouse expressing a Voltage Sensitive Fluorescent Protein (VSFP) in cortical layer 2/3 neurons. We induced a focal stroke (or sham) in the M1 (motor) region of the prefrontal cortex, approximately 2mm in diameter, and recorded Local Field Potentials (LFP) and fluorescence based voltage signals from layer 2/3 two weeks later. We observed reduced excitability in response to increasing Layer 5a stimulation in layer 2/3 of both M1, approximately 350µm ventral to the stroke border ($P<0.05$, 2-way ANOVA) and M2 (pre-motor), approximately 1mm ventral to the stroke border ($P<0.005$, 2-way ANOVA) compared to sham controls. The decreased excitability of the M2 region highlights synaptic reorganisation in a distal cortical region not directly affected by the initial injury. Whether this hypo-excitability during the second week post-stroke helps or hinders recovery remains to be determined.

Poster 5.54

Hippocampal place cell representations of effortful space

B. S. PORTER, C. K. YOUNG, and D. K. BILKEY
Department of Psychology, University of Otago, Dunedin, New Zealand

When navigating through an environment, it is important to consider the effort costs of available routes in order to minimise energy expenditure. The hippocampus has a unique functional cell type, called place cells, which fire selectively for a given location within an environment and are implicated in route planning and navigation. Place cells are also thought to play an important role in episodic memories; associating the *who* and *what* with *where* they occur in space. However little work has been done to investigate how place cells represent space, which is difficult to traverse, such as hills and mountains. It is possible that place cells associate given locations and the effort associated with those locations in order to aid navigation. We set out to investigate how place cells represent effortful space by recording hippocampal place cells in rats as they ran back and forth in a shuttle box for a small reward. To introduce effort, the shuttle box was tilted to three different pitches: flat, 15 degrees, and 25 degrees. We discovered two functionally distinct populations of place cells. One group was active on all three of the effort conditions but cell's firing rates changed significantly across each of the conditions. These cells may be tuned to represent the environment as a whole but are more selective to some conditions over others. The place cells of the second population fired for only one condition and were essentially inactive for the other two. These cells may be tuned to representing a given pitch to provide downstream neural structures with information about how steep, and thus how difficult, a space is.

Poster 5.55

Phenotypic characterisation of PSA-NCAM$^+$ cells in the adult human brain

H. C. MURRAY, M. E. V. SWANSON, B. V. DIERIKS, R. L. M. FAULL, and M. A. CURTIS
Department of Anatomy and Medical Imaging and Centre for Brain Research, University of Auckland, Auckland, New Zealand

Polysialylated neural cell adhesion molecule (PSA-NCAM) is a membrane bound glycoprotein that regulates cell-cell interactions and facilitates cell migration and plasticity. While commonly described in the neurogenic niches, we have recently demonstrated the widespread expression of PSA-NCAM in the adult human brain. In particular we identified expression in regions that are devoid of PSA-NCAM in the rodent brain such as the caudate nucleus and cerebellum. Furthermore PSA-NCAM load was significantly reduced in the entorhinal cortex of Alzheimer's disease cases (Murray et al., 2016). In this study we sought to characterize the phenotype of PSA-NCAM$^+$ cells in different regions of the human brain to further understand how this protein is involved in adult brain plasticity. Using fluorescent immunohistochemistry we identified PSA-NCAM$^+$ cells co-labelled with the mature neuron marker NeuN and markers of specific interneuron subpopulations such as calretinin, calbindin and parvalbumin. The proportion of interneurons expressing PSA-NCAM within a subpopulation differed between brain regions. Together this data suggests PSA-NCAM$^+$ cells in the adult human brain are mature interneurons and expression of PSA-NCAM may represent a specific mechanism of interneuron plasticity. As such these results indicate there are regional differences in interneuron plastic capacity which may explain the selective interneuron degeneration observed in disease states. We are currently investigating if the proportions of PSA-NCAM$^+$ interneurons are altered in different regions Alzheimer's disease.

Poster 5.56

Olfactory-targeted microparticles: a novel approach to bypass the blood-brain barrier

S. B. RIZWAN[1,3], S. B. YARRAGUDI[1], R. RICHTER[1], G. F. WALKER[1], and A. N. CLARKSON[2,3]
[1]School of Pharmacy, [2]Department of Anatomy, [3]Brain Health Research Centre, University of Otago, Dunedin, New Zealand

Delivery of drugs via the intranasal olfactory route is a non-invasive and practical method of bypassing the blood-brain barrier (BBB). However, targeted delivery and retention of drug formulations to the olfactory region is a major challenge due to its geometrical complexity and mucociliary clearance. Formulating drugs into particulate-carriers, specifically carriers with mucoadhesive properties can overcome this challenge by enabling targeted deposition of a greater dose-to-volume ratio of drug onto the olfactory epithelium for subsequent uptake by olfactory neurons. Recent modelling data indicates that particles 10–15µm in size show maximum deposition in the olfactory region, the target site for nose-to-brain drug absorption. The objective of this study was to develop a naturally occurring mucoadhesive polymer, Polymer-X, into 10–15µm sized microparticles for selective deposition in the olfactory region. We demonstrate that Polymer-X can be formulated as mucoadhesive microparticles with a mean particle size of 10µm. Using a human 3D-nasal replica cast we show that 10µm Polymer-X microparticles have a greater deposition in the olfactory region compared to 2µm microparticles. Based on these results, fluorescently-labelled dextran's (FITC-dextran) of varying molecular weights were selected as a model drug and incorporated into 10µm Polymer-X microparticles. Using porcine nasal mucosa we then demonstrate that FITC-dextran incorporated in microparticles can permeate the nasal mucosa in a size-dependent (molecular weight) manner. Histological studies show no evidence of toxicity to mucosa after microparticle exposure. Collectively, these findings demonstrate that 10–15µm sized Polymer-X microparticles have the potential to significantly enhance deposition and retention of drug molecules in the olfactory region for enhanced nose-to brain delivery

6.1

Risk of dementia in Parkinson's disease: Towards optimal short cognitive testing

K. HORNE[1,2], D. J. MYALL[2], L. LIVINGSTON[2,3], S. F. GRENFELL[2], T. R. MELZER[2,3,5], T. L. PITCHER[2,3], M. R. MACASKILL[2,3], T. J. ANDERSON[2,3,4,5], and J. C. DALRYMPLE-ALFORD[1,2,3,5]

[1]Department of Psychology, University of Canterbury, Christchurch, New Zealand
[2]New Zealand Brain Research Institute, Christchurch, New Zealand
[3]Department of Medicine, University of Otago, Dunedin, New Zealand
[4]Neurology, Christchurch Hospital, Christchurch, New Zealand
[5]Brain Research New Zealand, Universities of Auckland and Otago

Cognitive testing is used to identify Parkinson's (PD) patients at risk of dementia (PDD). To determine a short battery of tests sensitive to PDD risk, we used logistic regression to cull our 24-test battery to select two tests most sensitive to PDD progression over 4 years in each of 5 cognitive domains. That analysis identified map search, digit ordering (Attention), Stroop interference, Trails B (Executive), picture completion, Rey copy (Visuospatial), CVLT free recall, Rey-delay (Memory), DRS-2 similarities and category fluency (Language). Twenty-eight of 138 patients converted to PDD over 4 years; at baseline participants were classified as PD-MCI if showing two scores at -1.5SD for the reduced test list. These PD-MCI patients had a similarly high relative risk (RR) of PDD (7.1, 95%CI 3.1-16.3, p<0.0001) as the group classified as PD-MCI using the full test battery (RR=6.9, CI 2.5-18.9, p<0.001), compared to non-MCI PD patients. Even restricting a PD-MCI diagnosis to patients who had two impairments present only across two or more domains showed significant, albeit lower, RR (3.6, CI 1.3-10.3, p=0.015) than PD-MCI patients who had at least two impairments within a single domain (RR=7.0, CI 3.9-12.7, p<0.0001) with the restricted test battery. Thus, a short battery of sensitive cognitive tests can identify a group of PD patients at high risk of progression to PDD over 4 years; if validated it could be adopted by clinical research and targeted intervention studies. Out of sample validation and confirmation is now needed to confirm utility.

6.2

Maternal immune activation alters sensitivity to action-outcome contingency in adult rat offspring

J. MILLAR, D. BILKEY, and R. D. WARD

Department of Psychology, University of Otago, Dunedin, New Zealand

Epidemiological studies have provided convincing evidence for a role of maternal immune activation in the pathogenesis of schizophrenia. In recent years, several research groups have capitalised on this discovery and developed animal models such as the maternal immune activation (MIA) model that emulates many phenotypes characteristic of the disorder. In the present series of experiments we used the MIA model to examine motivation, a core component of the negative symptomology in schizophrenia. Contrary to what we expected, in the progressive ratio task which assesses an animals' willingness to work for a reward under increasing effort requirements we found that MIA rats appeared more motivated than controls. Subsequent tests showed that this seemingly enhanced motivation was not due to an overall increase in responding, nor due to enhanced attribution of incentive salience to reward associated responses. Instead, we found that the increased willingness to work exhibited by MIA animals was due to an inability to detect changes in the contingency between their behaviour and the resulting rewarding outcome. With regard to motivation, the experiments reported here are the first to subject the MIA model to a rigorous experimental analysis of behaviour by parsing apart underlying processes that give rise to the overt symptoms of the disease.

6.3

Mammillothalamic tract lesions decrease theta coherence between the anterior ventral nucleus and both prefrontal cortex and hippocampus in a spatial memory task

B. A. L. PERRY[1,3], S. C. BARNETT[1,3], J. LEE[1], J. J. HAMILTON[1,3], N. McNAUGHTON[4], and J. C. DALRYMPLE-ALFORD[1,2,3]

[1]Department of Psychology, University of Canterbury, Christchurch, New Zealand
[2]New Zealand Brain Research Institute, Christchurch, New Zealand
[3] Brain Research New Zealand, Universities of Auckland and Otago, New Zealand
[4]Department of Psychology, University of Otago, Dunedin, New Zealand

In humans, damage to the mammillothalamic tract (MTT) is the most consistent predictor of amnesia following thalamic stroke. We tested the prediction that MTT damage results in functional disruption across key structures in the extended hippocampal memory system. Local field potentials were recorded during the wait time between arm choices in the centre of a radial arm maze test of working memory. Rats with MTT lesions showed impaired spatial working memory in the maze. MTT lesions (n=14) also significantly reduced theta frequency coherence (4-12Hz) between the anterior thalamic nuclei (ATN) and the prefrontal cortex (PFC), particularly at higher frequencies, as well as the peak frequency coherence (9.2Hz) shown by sham controls (n=11). Only peak theta frequency coherence (8.8Hz) between ATN and hippocampus (HPC) was affected by MTT lesions. Gamma frequency coherence (55-100Hz) between ATN and PFC was also depressed in MTT rats. No significant effects were observed for PFC-HPC coherence or for beta frequencies (13-30Hz) between any structures. This is the first evidence of disrupted functional connectivity between major neural structures of the extended hippocampal system as a result of MTT lesions; and provides initial support for the view that MTT lesions impact memory due to a disruption to theta-based temporal packaging of information passing to the prefrontal cortex and hippocampus via the anterior thalamic nuclei.

7.1

The fine-scale structure of spontaneous synaptic activity in the developing mouse visual cortex

J. E. CHEYNE, N. ZABOURI, and C. LOHMANN

Synapse and Network Development Laboratory, Netherlands Institute for Neuroscience, Amsterdam, The Netherlands

Neurons in the developing brain are spontaneously active before the onset of sensation. This spontaneous activity is crucial for development of the specific neuronal networks that are required for normal brain function. Here I will describe how we combined dendritic calcium imaging with whole cell electrophysiology *in vivo* to map synaptic inputs during spontaneous network events on the dendritic tree. These experiments showed that synaptic inputs are organized with subcellular precision already before eye opening. Our current aim is to reveal the fundamental logic of this organization, how it is set up during development and what neuronal computations it may serve.

7.2

Leptin resistance: Cause or consequence of hypothalamic inflammation?

A. TUPS[1,2], A. BOUCSEIN[1,2], N. SKINNER[1], and M. RIZWAN[1]
[1]Centre for Neuroendocrinology, Brain Health Research Centre, Department of Physiology, University of Otago, Dunedin, New Zealand
[2]Department of Animal Physiology, Philipps University Marburg, Marburg, Germany

Metabolic inflammation in the hypothalamus might be causative for the development of overnutrition-induced metabolic syndrome and related disorders, such as obesity, leptin and insulin resistance, and type 2 diabetes. We established that nutritive and genetic inhibition of the IκB kinase β (IKKβ)/nuclear factor-κB (NF-κB) pathway, the main mediator of hypothalamic inflammation, improves these metabolic impairments in diet-induced obese (DIO) and leptin-deficient mice. Genetic inhibition of the IKKβ/NF-κB signaling pathway in the arcuate nucleus, via specific adeno-associated virus serotype 2-mediated overexpression of IκBα, which inhibits NF-κB nuclear translocation, attenuated high-fat diet-induced body weight gain, body fat mass accumulation, increased energy expenditure, and reduced arcuate suppressor of cytokine signaling 3 expression, indicative for enhanced leptin signaling. One key question in metabolism research is whether leptin resistance is caused by hypothalamic inflammation, or whether hypothalamic inflammation is a consequence of leptin resistance because leptin acts also as a pro-inflammatory hormone. A loss of leptin sensitivity as determined by the ability of leptin to activate its transcription factor (signal-transducer and activator of transcription) in the arcuate nucleus occurred already within 24 hours of high-fat feeding which coincides with the onset of hypothalamic inflammation. We furthermore discovered that high-fat diet disrupts circadian regulation of leptin sensitivity. Since pro-inflammatory signalling pathways are an important component of the mammalian circadian clock and activation of these pathways is known to disrupt circadian rhythms, collectively these data support the hypothesis that high-fat diet-induced leptin resistance and the onset of obesity is caused by hypothalamic inflammation.

7.3

Localization of glutamatergic synapses around the sensory receptors in the mammalian inner ear during development

M. BARCLAY[1,4] ,N. R. JAMES[1,4], J. M. MONTGOMERY[1,4], A. McMORLAND[3,4], and P. R. THORNE[1,2,4]
[1]Department of Physiology, [2]Section of Audiology, [3]Department of Sport and Exercise Science, [4]Centre for Brain Research, University of Auckland, Auckland, New Zealand

Inner hair cells (IHCs) in the mammalian cochlea transduce sound waves into electrical impulses and differential distribution of glutamatergic synapse structure around the base of the IHC appears to be important for encoding sound intensity information. This study examines the development of IHC innervation, particularly localization of synapses around the IHC, localization of synapse pruning and changes in synapse structure prior to and after the onset of sound mediated stimulation of the IHC at postnatal day (P) 12. Cochlea tissue was dissected from P6 – 21 mice and the expression of RIBEYE and GluA2, components of the vesicle release machinery and AMPA receptor complexes respectively were examined along the length of the cochlea using immunofluorescence and confocal microscopy. Custom written algorithms developed in Python were used for image analysis and mapped these synaptic proteins around the basolateral membrane of the IHC. These studies showed differential distribution of synapses along the length of the cochlea, with a greater density in the mid-turn region. Synapse pruning that occurs between P6 and P12 was localized to specific regions of the IHC and synapse structure was variable at birth, but this variability decreased through early development and by the onset of hearing it appeared established and consistent. These data provide a blueprint of synapse development in the cochlea and will be used for future studies that examine how developmental insults affect synapse structure in the cochlea.

7.4

Temporal rhythms of metabolic pathways in the hypothalamus

A. BOUCSEIN, M. RIZWAN, N. SKINNER, and A. TUPS
Department of Physiology, Centre for Neuroendocrinology, University of Otago, Dunedin, New Zealand

Synchronisation between biological temporal clocks and metabolic responses is crucial for the survival of many organisms. Here, we investigated whether WNT signalling as well as leptin signalling, two important pathways in the control of energy metabolism, are modulated by temporal rhythms in the hypothalamus. We analysed the seasonal and circadian regulation of WNT signalling in the Djungarian hamster (*Phodopus sungorus*), a seasonal mammal that exhibits profound annual changes in energy metabolism. First, we examined mRNA expression of key WNT pathway components in the arcuate nucleus by *in situ* hybridisation. We detected elevated expression of several genes of the WNT pathway in hamsters acclimated to long day (LD) compared with short day (SD) photoperiod, as well as circadian regulation of WNT target genes. Next, we analysed the effect of photoperiod as well as leptin on the activation of the WNT co-receptor LRP-6 by immunohistochemistry. The number of activated phospho-LRP-6-(Ser1490)-immunoreactive cells in the arcuate nucleus was elevated during LD relative to SD, as well as after leptin (2 mg/kg body weight) compared with control treatment in animals from both photoperiods. These findings suggest that WNT signalling is regulated in a seasonal and circadian manner in the adult brain. Furthermore, they provide evidence that this pathway plays a key role in the neuroendocrine integration of the leptin signal. We next investigated whether regulation of leptin sensitivity is regulated in a circadian manner in mice and potentially influenced by high fat diet (HFD), by measuring the ability of leptin to induce leptin signalling in the arcuate nucleus, Surprisingly, leptin resistance was not universal, but varied diurnally, with a circadian return of normal leptin sensitivity.

8.1

Analysis of information encoding and dynamics in optically recorded cortical circuits

S. R SCHULTZ
Department of Bioengineering, Imperial College, London, United Kingdom

In recent years, technology for large-scale recording of neural circuit dynamics, at single cell resolution, has progressed extremely rapidly. Several international initiatives, including the US NIH BRAIN Initiative, mean that we are likely to see further developments, including the ability to manipulate as well as read out neural ensemble activity. As well as enhancing our understanding of numerous basic questions in systems neuroscience, we can hope that these techniques are likely to be of translational benefit, by allowing the characterisation of changes to circuit behaviour in mouse models of neurodegenerative disorders to be studied in great detail and across scales. Scalable data analysis tools capable of taking into consideration patterns of neural ensemble activity, however, become a limiting factor once neural population sizes exceed a few tens of neurons. In the past, I have developed information theoretic methods for analysing how information is represented in spike trains fired by small ensembles of neurons. In this talk, I will describe several approaches we are taking to scale these approaches up to tens and hundreds of neurons recorded simultaneously through two photon calcium imaging. We take two quite different approaches. In the first approach, we consider the calcium time series from the neural ensemble as a multivariate continuous time series, and employ approaches from nonlinear dynamics, together with dimensionality reduction. In the second, we use a calcium transient detection algorithm to instead represent the data as a digitized multineuron spike train, and make strong but testable assumptions about the underlying variability. In the talk, I will describe the application of these methods to data from a number of cortical circuits: neocortical, archicortical (hippocampus) and the cerebellar cortical circuit.

8.2

Integrating reliable, cost-effective, open-source hardware for high throughput neurophysiological, optogenetic and behavioural experimentation in rodents

C. K. YOUNG
Department of Psychology, University of Otago, Dunedin, New Zealand

With the rapid development of manufacturing processes, miniaturisation and capabilities of consumer-level electronics, many complex and costly research challenges can be addressed using non-commercial, cost-effective solutions. There has been a steady stream of published open-source solutions for scientific research in general, and particularly in neurophysiology. However, past efforts were often plagued by limited accessibility of parts, resources or expertise. Open Ephys is an initiative to drive and provide open-source tools for routine neuroscience research, with a strong world-wide community of 80+ laboratories engaged in research targets ranging from humans to rodents. With a strong community, ongoing software and hardware improvements are made at a steady pace. To take advantage of the advancements in these open-source technologies, I have constructed and combined an Open Ephys acquisition system (up to 256 channel of neurophysiology data), Intan headstages (32 channels with 3-axis accelerometer), PulsePal (programmable stimulus generator) and Cyclops (ultra-precise, programmable LED driver) to create an integrated experimental system for examining neural correlates of executive control over motor output across limbic, basal ganglia and other functionally linked brain regions. I have completed preliminary testing of an integrated system capable of 32-channel recording with 8 channel digital input/output, and programmable stimulus generation for implementing electrical or optical stimulation. I am currently in the process of implementing real-time position tracking, close-loop stimulation, actuating behavioural apparatus, and acquisition of field potential and spiking data from behaving rats. The ultimate goal is to construct user-friendly, flexible experimental systems capable of supporting high-throughput, state-of-the-art research at significantly reduced costs; thus providing a competitive edge by being able to do more research with less cost.

8.3

Detailed modelling of neuronal calcium dynamics to enable validation of the NVU

T. VAN GINKEL[1,2], T. DAVID[1,2], and M. PLANK[3]
[1]Department of Mechanical Engineering, [2]University of Canterbury High Performance Computing, [3]Department of Mathematics and Statistics, University of Canterbury, Christchurch, New Zealand

Neurovascular coupling (NVC) describes the vasculature's ability to regulate cerebral perfusion based on neuronal activity. The cells involved in the NVC process are neurons, glial cells and vascular cells, which together comprise a neurovascular unit (NVU). Our research group has developed a model of the NVU with high spatial and temporal resolution to quantify the process of neuronal activation to vascular response. However, the majority of ionic concentrations and fluxes modelled, and by extension the model, are difficult to verify experimentally. While neuronal calcium concentrations can be verified with existing experimental data, the current NVU utilises a simplified model of the calcium dynamics involved. We use biophysically realistic models of calcium dynamics in cerebral Purkinje cells to implement neuronal calcium dynamics into the NVU. The model presented uses a compartmentalised lumped parameter approach, comprising the extracellular space, synaptic cleft, cytosol and endoplasmic reticulum (ER). We show that the model is able to generate a physiologically realistic calcium profile in the cytoplasm in response to neuronal activation through a glutamate pulse. This is achieved through hypo polarisation of the cell membrane, followed by draining of the calcium stored in the ER into the cytoplasm. Upon removal of the glutamate input stimulus, return to equilibrium is observed on a physiologically realistic timescale. This is the first component of the NVU that can be readily verified experimentally. The results of the neuronal calcium model generated are more physiologically accurate than those of the currently implemented model.

8.4

Network plasticity in the sensory cortices

M. J. SPRIGGS[1,2], R. L. SUMNER[1], S. MUTHUKUMARASWAMY[1], and I. J. KIRK[1,2]
[1]School of Psychology, Centre for Brain Research, [2]Brain Research New Zealand, University of Auckland, Auckland, New Zealand

Disrupted synaptic plasticity and concomitant disruption of neural networks is increasingly being recognized as central to the neuropathology of neurological disorders, such as Alzheimer's disease and Schizophrenia. However, the underlying mechanisms remain largely unexplored. This study aims to assess whether individual differences in network plasticity can be identified using electroencephalography (EEG) in the hope that this inexpensive, non-invasive technique could be used to identify disease related processes in clinical settings. Dynamic Causal Modelling (DCM) was used to model experimentally induced changes in intrinsic and extrinsic connectivity within sensory processing hierarchies across two event related EEG paradigms- The human Long Term Potentiation (LTP) paradigm, and the roving Mismatch Negativity (MMN) paradigm. As both paradigms are understood to index NMDA-dependent plasticity, it was hypothesized that individual differences in network plasticity would be consistent across the two paradigms. To assess this, participants were genotyped for the *BDNF* Val66Met polymorphism. The *BDNF* Met allele decreases the secretion of Brain Derived Neurotrophic Factor (BDNF), an important mediator of synaptic plasticity. Met allele carriers were therefore expected to exhibit reduced plasticity at lower levels of the sensory processing hierarchies. Bayesian Model Comparison revealed that both paradigms modulated extrinsic connectivity between regions of the processing hierarchies. Additionally, while this was seen in forward connections for *BDNF* Val homozygotes, *BDNF* Met carriers demonstrated modulation of backward connections, suggesting a potential top-down compensation for decreased BDNF secretion. Importantly, the genotype effect was consistent across both paradigms. This supports the hypothesis that the EEG paradigms index synaptic plasticity, and that network modelling may be used to identify individual differences, and potentially disease-related changes, in network plasticity.

8.5

Unsupervised classification of excitatory neurons in layer 3 of the piriform cortex using morphological, electrical and synaptic properties

J. J. ROBERTSON and J. M. BEKKERS
Eccles Institute of Neuroscience, John Curtin School of Medical Research, Australian National University, Canberra, Australia

The piriform cortex is the first cortical site of odour processing. In order to understand how odour information is processed in the piriform cortex, it is helpful to first characterise the cell types involved. Previous studies have classified the excitatory neurons in layer 2 and the GABAergic neurons in all layers of the piriform cortex. This study aimed to rigorously define the classes of excitatory neurons in layer 3. Experiments used acute slices from P18-25 GAD67 GFP mice, in which we were able to identify excitatory neurons by their lack of GFP expression. We recorded the morphological and electrical properties from 59 layer 3 excitatory neurons. To determine the number of classes we optimised the Calinski-Harabasz index, the Silhouette index, the Gap measurement and the Davies-Bouldin index for four commonly used clustering algorithms. The Kruskal-Wallis test was used to determine significance. We determined that there are two extreme classes of excitatory neurons in layer 3 of the piriform cortex: deep pyramidal (DP) cells and excitatory multipolar (EM) cells. The EM and DP cells differed significantly ($p<0.05$) in morphology, electrophysiology and synaptic connectivity, suggesting that they have different roles in odour processing. Interestingly, there also appeared to be a gradient of intermediate neuronal classes between the two extremes, as determined using the Dip Test. This study provides the first rigorous characterisation of the excitatory cells in layer 3 of the piriform cortex, identifying classes of excitatory neurons that are likely to be important for the cortical processing of odours.

9.1

High-intensity training enhances executive function in children

D. M. MOREAU and K. E. WALDIE
Centre for Brain Research, University of Auckland, Auckland, New Zealand

Physical exercise has shown to elicit improvements in several measures of cognition. Traditionally, this effect has been observed following aerobic exercise interventions, that is, sessions of moderate-intensity exercise maintained over time. Here, we present evidence demonstrating that short bursts of exercise based on high-intensity training (HIT) can produce similar cognitive improvements. Specifically, HIT induced substantial gains in measures of cognitive control and working memory capacity, and this effect was moderated by *BDNF* genotype, with met^{66} carriers more likely to benefit from exercise. In addition, our results indicate that HIT helps downregulate elevated resting heart rate, thus benefiting more largely individuals who need it most. These findings complement previous literature linking physical exercise to cognitive enhancement, and provide a more detailed account of the mediating factors of improvement. Overall, this line of research suggests promising alternatives to enhance cognition, via shorter, more potent exercise regimens.

9.2

When do we perceive subtle facial expressions?

J. MAO[1], P. M. CORBALLIS[1], and J. SOLLERS[2]
[1]School of Psychology, [2]School of Medicine, University of Auckland, Auckland, New Zealand

Facial expression is essential to human social communication, and there is considerable research interest in psychology and psychophysiology in understanding how emotion is conveyed on the face. Although most facial expressions are easily to perceive by an observer, brief and subtle (with lower intensity levels) expressions can sometimes hardly be noticed. Therefore, studying those expressions at neurological using psychophysiological measures such as EEG, is a promising new approach to the detection and characterization of subtle expressions. The study used an oddball paradigm. 18 participants viewed facial expressions of happiness (at 20% and 40% intensity levels), anger (at 20% and 40% intensity levels), disgust (at 100% intensity level) and neutral at different intensity levels. All expressions were displayed for 300ms.Our results suggested that a) at early time window (N170), anger evoked larger N170 compared to happiness regardless of the intensity levels; and b) expressions with higher intensity level (40%) produce larger FcEP (frontocentral emotional positivity) component. Taken together, our result suggested that the processing of emotion category started as early as 170ms and the processing of expressional intensity level started afterwards at round 250-350ms.

9.3

The effects of kappa opioid agonists on the novel object recognition task

S. WELSH[1], T. PRISINZANO[2], and B. KIVELL[1]
[1]*Centre for Biodiscovery, Victoria University of Wellington, Wellington, New Zealand*
[2]*Department of Medicinal Chemistry, University of Kansas, Kansas, United States of America*

Kappa opioid protein receptors (KOPr) are widely expressed throughout the central and peripheral nervous systems. Activation of these receptors has been shown to produce analgesia without activating the brains reward system meaning they have little abuse potential. Salvinorin A, a non-nitrogenous diterpene isolated from the psychoactive plant *Salvia divinorum,* is a potent and selective KOPr agonist. Unfortunately, the duration of action of Salvinorin A is only short making it undesirable as a therapeutic agent. Structural analogues of Salvinorin A have shown an increase in duration of action whilst maintaining analgesic and anti-addictive properties. Because KOPr activation has been shown to modulate learning and memory we chose to evaluate the effects of our novel KOPr agonists on novel object recognition in rats using a within-subjects design. This test evaluated the time spent interacting with a novel object, with a decrease in interaction time indicative of impaired learning and memory. Adult male Sprague Dawley rats were familiarised with two copies of the same object (A1 and A2) and presented with the familiar and a novel object (A1 and B) the following day. The time spent interacting with the novel object (B) in relation to the familiar object A1 was recorded. We show that the traditional KOPr agonist, U50,488, produced a significant impairment in recognition memory when compared to vehicle. We evaluated dose effects of Salvinorin A and analogues messily Salvinorin B, ethynyl Salvinorin A, and broom Salvinorin A and no memory impairment was seen. This, along with data on analgesia and various side effects, means these novel KOPr agonists have promise as future non-addictive therapeutics.

9.4

Source localization of stop- and conflict-related rhythmicity

S. M. SHADLI[1], I. J. KIRK[2], and N. McNAUGHTON[1]
[1]*Department of Psychology, University of Otago, Dunedin, New Zealand*
[2]*School of Psychology, University of Auckland, Auckland, New Zealand*

Goal conflict specific rhythmicity (GCSR), over a range of versions of the stop signal task (SST) is a biomarker for an anxiolytic-specific process. To place it within the existing neuropsychology of the Behavioural Inhibition System, we estimated the anatomical source of GCSR and of stopping. Our hypotheses were that: a) two different neural networks would be activated to generate stopping in the SST: right inferior frontal gyrus (rIFG); and preSMA (involving medial frontal gyrus) depending on the response strategy; and b) GCSR would involve multiple neural networks, including rIFG; medial frontal gyrus and superior frontal gyrus. We carried out two experiments. One used a 32 channel EEG system with high participant numbers. The second used a high resolution EEG (128 channel) system with low participant numbers. The neural source of stop related 4-12 Hz frequency was rIFG in block-1, where the stop signal reaction time (SSRT) was slower and medial frontal gyrus or pre-SMA in block-3 of SST, where the SSRT was faster, as expected. The neural source for GCSR-band rhythmicity in block-1 of SST was right frontal gyrus with the involvement of superior frontal gyrus. In block-3 of SST, we observed right inferior frontal gyrus as the key source of GCSR with the involvement of medial frontal gyrus. So, our stop related source localization was consistent with previous findings and the GCSR source was similar but more diffuse in the human brain suggesting that conflict processing involves parallel circuits to stopping in the human brain. Further imaging experiments, particularly with fMRI, are needed to unravel the neural source of GCSR.

10.1

APP overexpression causes Aβ-independentneuronal death through intrinsic apoptosis pathway

L. BELLUSCIO, N. CHENG, A. GUMASTE, and S. JIAO
Developmental Neural Plasticity Section, National Institutes of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, United States America

Accumulation of amyloid-β (Aβ) plaques is a hallmark of Alzheimer's disease (AD) and thought to be the cause of neurodegeneration. However, the correlation between Aβ plaque load and cognitive dysfunction is poor, raising questions about the Aβ hypothesis as the sole basis for disease. Since olfactory loss can occur early in AD we sought to determine the underlying mechanism as it relates to AD. We utilized a previously developed *in vivo* mouse model that expressed a humanized form of the amyloid precursor protein (hAPP) in olfactory sensory neurons (OSNs) and revealed clear cell-autonomous apoptosis. Together with additional transgenic lines and a combination of molecular and biochemical assays we analyzed the basis of this OSN neurodegeneration. Here we show, in two distinct mouse models that hAPP-induced apoptosis of OSNs occurs early and is independent of Aβ, highlighting the presence of other pathogenic mechanisms. We further demonstrate that hAPP-induced apoptosis is mediated by the intrinsic apoptosis pathway which is linked to mitochondrial dysfunction and implicates cell stress as a potential factor. These findings support olfactory disruption as an early indicator of AD and present a mechanistic basis for the associated olfactory loss that may provide insight for future therapeutic targets.

10.2

Brain arginine metabolism is altered in patients with schizophrenia

P. LIU[1,4], Y. JING[1,4], N. D. COLLIE[1,4], B. DEAN[5], D. K. BILKEY[2,4], and H. ZHANG[3,4]
[1]Department of Anatomy, [2]Department of Psychology, [3]School of Pharmacy, [4]Brain Health Research Centre, University of Otago, Dunedin, New Zealand
[5]The Molecular Psychiatry Laboratory, The Florey Institute for Neuroscience and Mental Health, Melbourne, Australia

L-arginine is a versatile amino acid with a number of bioactive metabolites. Altered arginine metabolism has been implicated in the pathogenesis of schizophrenia, however based on the information obtained from studies of a single metabolic pathway. The present study, for the first time, systematically compared the metabolic profile of L-arginine in the frontal cortex (Brodmann's area 8) obtained post-mortem from individuals with schizophrenia and age- and gender-matched non-psychiatric controls (n = 20/group). The enzyme assays revealed no change in total nitric oxide synthesis (NOS) activity, but significantly increased arginase activity in the schizophrenia group. Western blot showed reduced endothelial NOS protein expression and increased arginase II protein level in the disease group. High performance liquid chromatography and liquid chromatography/mass spectrometric assays confirmed significantly reduced levels of GABA, but increased agmatine concentration and glutamate/GABA ratio in the schizophrenia cases. Regression analysis indicated positive correlations between arginase activity and the age of disease onset and between L-ornithine level and the duration of illness. The present study provides further evidence of altered brain arginine metabolism in schizophrenia. The findings enhance our understanding of the pathogenesis of schizophrenia and may lead to the future development of novel preventions and/or therapeutics for the disease.

10.3

Impaired expression of GABA transporters in the human Alzheimer's disease hippocampus, subiculum, entorhinal cortex and superior temporal gyrus

T. E. FUHRER[1], T. H. PALPAGAMA[1], H. J. WALDVOGEL[1], B. J. L. SYNEK[1,2], C. TURNER[1,2], R. L. FAULL[1], and A. KWAKOWSKY[1]

[1]Centre for Brain Research, Department of Anatomy and Medical Imaging, University of Auckland, Auckland, New Zealand

[2]Department of Anatomical Pathology, LabPlus, Auckland City Hospital, Auckland, New Zealand

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain and plays an important role in regulating neuronal excitability. GABA reuptake from the synapse is dependent on specific transporters - mainly GAT-1, GAT-3 and BGT-1 (GATs). There are no previous studies investigating the role of these transporters in the human hippocampus in Alzheimer's disease (AD), a neurodegenerative disorder that affects millions of people worldwide. The aim of this project is to use immunohistochemistry and confocal imaging to investigate the region and layer specific density of GAT-1, GAT-3 and BGT-1 protein expression in the hippocampus, entorhinal cortex and superior temporal gyrus of control and AD brains. We found a significant increase in BGT-1 expression associated with AD in all layers of the dentate gyrus, in the stratum pyramidale of the CA2 and CA3 and the superior temporal gyrus. In AD there was a significant decrease in GAT-1 expression in the entorhinal cortex and superior temporal gyrus. We also found a significant decrease in GAT-3 immunoreactivity in the stratum pyramidale of the CA1 and CA3, the subiculum and entorhinal cortex. The GABAergic system is a promising drug target for AD and therefore, understanding GABA transporter expression changes in the AD brain will help provide guidance into selecting drugs that either antagonize or agonize these transporters, and thereby regulate the amount of GABA within the synaptic and extrasynaptic space, altering neuronal excitability. These observations indicate that the expression of the GATs shows brain region and layer specific alterations in AD, suggesting a complex activation pattern and possibly co-regulation of different GATs during the course of the disease.

10.4

Epidemiology of Parkinson's in New Zealand: sex, age, and future burden

D. J. MYALL[1], T. L. PITCHER[1,2], M. R. MACASKILL[1,2], J. F. PEARSON[3], C. LACEY[4], J. C. DALRYMPLE-ALFORD[1,5,6], and T. J. ANDERSON[1,2,6,7]

[1]New Zealand Brain Research Institute, Christchurch, New Zealand

[2]Department of Medicine, [3]Biostatistics and Computational Biology Unit,

[4]Department of Psychological Medicine, University of Otago, Christchurch, New Zealand

[5]Department of Psychology, University of Canterbury, Christchurch, New Zealand

[6]Brain Research New Zealand, Universities of Auckland and Dunedin, New Zealand

[7]Department of Neurology, Christchurch Hospital, Christchurch, New Zealand

We present the first nationwide estimates for the prevalence and incidence of Parkinson's in New Zealand (NZ), including examining the effects of sex and age. Information on Parkinson's-related medications was extracted from the Pharmac database (January 2005 to December 2014). The number of people with Parkinson's was estimated using drug-tracing methods, calibrated using known diagnoses for a large subset of individuals. Prevalence and incidence was calculated using Statistics NZ population counts. The 2013 prevalence of Parkinson's in NZ was 220 per 100,000 population. As expected, age-standardised prevalence rates were higher for males (ratio 1.6:1). Incidence was 30 per 100,000 person-years, again higher in males (ratio 1.7:1). Incidence and prevalence by age increased exponentially until 75 years, followed by deceleration, dropping sharply from 85 years. This might be because the pool of people susceptible to developing Parkinson's has been depleted by that age, or because people in that age group are under-diagnosed and/or are receiving reduced levels of treatment. The decreasing incidence in the oldest age groups impacts substantially on predictions of future disease burden. Under a variety of future assumptions, despite the ageing overall population we predict that in coming decades, following a period of increasing prevalence, the burden of Parkinson's will begin to plateau rather than continue to increase monotonically.

10.5

Aberrant pericyte signaling in Huntington disease

T. I-H. PARK, E. H-W. KIM, L. C. D. SMYTH, J. RUSTENHOVEN, R. L. M. FAULL, and M. DRAGUNOW
Centre for Brain Research, University of Auckland, Auckland, New Zealand

Neurovascular changes are now recognized to play a pivotal role in the pathophysiology of neurodegenerative diseases such as Huntington disease (HD), but the mechanisms remain elusive. HD is caused by a genetic mutation resulting in a mutant huntingtin protein (mHtt), and this study investigates whether this mutation affects the neurovascular pericytes and how any changes might lead to the causation and/or progression of HD. Immunohistochemical and qRT-PCR examination of post-mortem normal and HD human brains revealed a higher blood-vessel density in HD compared to control in the caudate nucleus (CN) and the temporal gyrus (TG; $p < 0.001$). This data corroborated previous reports in mice and human studies, however, for the first time we found there was an overall decrease in the level of PDGFRβ in HD brains, a key receptor and phenotypic marker for pericytes. In HD brains, PDGFRβ staining per $CD31^+$ endothelial cells were at 30% and 50% levels compared to that of normal CN and TG respectively ($p < 0.001$). Furthermore, mHtt aggregates were found not only in neurons, but also in pericytes of HD brains, suggesting that mHtt may also affect neurovascular pericytes. These *in situ* findings were recapitulated *in vitro*, with the primary human pericytes isolated from HD brains showing lower levels of PDGFRβ expression and the presence of mHtt within the cell. These results confirm the expression of mHtt in HD pericytes *in vivo* and *in vitro*, suggesting that pericytes might be involved in the etiology of HD.

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11.1

B. HARRISON
Department of Psychiatry, University of Melbourne, Melbourne, Australia

11.2

Language, gesture, and handedness: Independent lateralized networks

M. C. CORBALLIS, P. M. CORBALLIS, and I. HABERLING

School of Psychology, University of Auckland, Auckland, New Zealand

We collected fMRI images in selected regions of the frontal, temporal and parietal areas in 46 left- and 46 right-handers while they performed language tasks (word generation, synonym judgments) and watched actors making manual gestures (pantomimes, sign language). We computed laterality indices from the areas activated by the different tasks, subjected these indices to factor analysis. This yielded three orthogonal factors, implying three different lateralized networks. One could be identified as a language network in temporal and frontal areas, another as an action-observation network gesture largely overlapping with the language network, and the third as an action-observation network distributed through parietal regions. Handedness was associated only with the third of these networks. These results suggest an evolutionary scenario in which the primate mirror neuron system became increasingly lateralized, and fissioned onto subsystems with one mediating language, one mediating the understanding of manual actions, and one associated with hand preference and perhaps associated with the use of tools. Factor analysis of laterality indices may be a useful way to discover the nature and number of lateralized networks, and understand their evolution through simpler systems.

11.3

Amyloid imaging and cognition in Parkinson's disease: Interim report

T. R. MELZER, R. J. KEENAN, D. J. MYALL, G. KAUR, L. LIVINGSTON, K. HORNE, S. MARSH, M. R. MACASKILL, J. C. DALRYMPLE-ALFORD, and T. J. ANDERSON

New Zealand Brain Research Institute, Christchurch, New Zealand

Dementia causes the greatest burden for patients with Parkinson's disease (PD) and their families and eventuates in about 80% or more of these patients. While cortical spread of misfolded α-synuclein protein is an important neuropathology, Alzheimer neuropathology, including accumulation of misfolded beta-amyloid, may also contribute to the emergence of dementia in PD (PDD). As part of an ongoing study, we examined amyloid accumulation in the brain, using 18F-Florbetaben positron emission tomography (PET) imaging, and its relationship to cognition in PD, focusing on patients with mild cognitive impairment (PD-MCI) who are known to be at high risk of PDD. Thus far, 50 of a planned 125 PD participants have completed Florbetaben PET imaging and neuropsychological assessments. Four PD patients were classified as having normal cognition (PDN), 41 with mild cognitive impairment (PD-MCI), and five with PDD. All four PDN patients were amyloid negative, but 15% (6/41) of PD-MCI, and 60% (3/5) of PDD patients were amyloid positive. The rate of amyloid positivity in PD-MCI was clearly lower than that observed in cohorts of amnestic MCI patients (~50-70%), suggesting different underlying neuropathology in the majority of PD-MCI cases. Despite the small number in the PDD group, dementia associated with PD can appear in the absence of amyloid accumulation, although it may be an additional factor in some patients. These preliminary findings suggest that other pathologies (e.g. a-synuclein, tau, vascular damage) may have a more predominant role than amyloid accumulation for the development of cognitive impairment in PD.

11.4

The corpus callosum in the human brain: measurements and findings

E. LUDERS
University of California Los Angeles School of Medicine, Los Angeles, United States of America

The corpus callosum is the largest fiber tract in the human brain, connecting the two hemispheres through more than 200 million fibers. Rapid technological developments in the field of neuroimaging and brain mapping have led to an exponential increase in the number of *in vivo* investigations exploring callosal morphology. This study tested a newer computational approach capturing the thickness of the corpus callosum with a high regional specificity at 100 equidistant points. More specifically, a sample of 72 healthy subjects (36 men, 36 women), aged between 30 and 69 years, was analyzed to investigate the impact of aging on callosal morphology. All findings were corrected for multiple comparisons using permutation testing with 10,000 iterations. Significant negative correlations ($p<0.05$) between chronological age and point-wise callosal thickness were observed across the callosal surface as evidenced in detailed color-coded maps. More specifically, the corpus callosum seems to be thinner in older people, with pronounced age effects in anterior callosal sections (corresponding to the rostrum, rostral body, and anterior midbody) and more subtle effects in posterior callosal sections (corresponding to the isthmus). Significant positive correlations were completely absent. Altogether, the study illustrates the suitability of the callosal thickness approach, revealing the direction, magnitude, and significance of the examined effects with a regional specificity that is much higher (100 data points) than yielded in most traditional approaches based on callosal parcellation and subsequent area measurements (about 5-7 data points).

11.5

The Simpson's paradox and fMRI: What we talk about when we talk about functional connectivity

R. ROBERTS[1], S. HACH[1], L. TIPPETT[1,2], and D. R. ADDIS[1,2]
[1]School of Psychology and Centre for Brain Research, [2]Brain Research New Zealand, University of Auckland, Auckland, New Zealand

Task-related functional connectivity (*fc-MRI*) indexes the interaction of brain regions during cognitive tasks. Two general classes of methods exist to investigate *fc-MRI*: the most widely-used method calculates temporal correlations between voxels/regions *within* subjects, and then determines if within-subject correlations are reliable across subjects (*ws-fcMRI*); the other calculates the average (BOLD) signal within voxels/regions and then performs correlations *across* subjects (*as-fcMRI*). That is, while both methods rely on correlational techniques, the level at which correlations are calculated are fundamentally different. While conceptually distinct, it is not known how well these two methods of *fc-MRI* analyses converge on the same findings. The current study addresses this question across a number of analyses. Using default-mode network regions as seeds, results showed only a weak association between *as-fcMRI* and *ws-fcMRI.* Follow-up analyses showed that the strength of agreement between the techniques is contingent on whether correlations are calculated between regions from the same functional network, or between regions from different functional networks. Lastly, a novel *fcMRI* technique is introduced that combines within-subject correlations with the multivariate approach of partial least squares (PLS) analyses. This approach is compared to standard seed PLS (an *as-fcMRI* method). Overall, the results suggest that the findings of *as-fcMRI* do not always map onto those from *ws-fcMRI*, and in some cases produce effects in the opposite direction (a Simpson's Paradox).

11.6

White matter changes after joint replacement in people with knee osteoarthritis

S. SHARMA[1], G. M. LEWIS[1], D. A. RICE[1,2], and P. J. McNAIR[1]

[1]Health and Rehabilitation Research Institute, Auckland University of Technology, Auckland, New Zealand

[2]Waitemata Pain Service, Department of Anaesthesiology and Perioperative Medicine, North Shore Hospital, Auckland, New Zealand

Chronic pain has been associated with structural and functional alterations in both grey and white matter in the brain. Little is known about neuroplastic changes in the brain following relief from chronic pain, such as that commonly seen following joint replacement surgery. We investigated grey and white matter in people with knee osteoarthritis before and after joint replacement surgery. Twenty patients who were scheduled to have knee replacement surgery were recruited. Structural MRI, fMRI (during rest), and DTI analyses were performed before (PREOP) and 6 months after surgery (POSTOP). Findings: Fractional anisotropy (FA) of white matter pathways was significantly greater in the POSTOP group compared to the PREOP group ($p < 0.05$). There were no structural differences, as determined by voxel based morphometry, or differences in resting state connectivity in the default mode network or the sensorimotor network. At 6 months post-knee replacement surgery, microstructural changes in white matter occurs despite no structural changes in grey matter or resting state networks. This suggests that white matter changes are amongst the first plastic changes to occur at 6 months post-surgery.

11.7

Clinical translation of Chemical Exchange Saturation Transfer (CEST) MRI for imaging glucose

C. MORGAN[1,2,3,4], D. ATKINSON[5,9], S. WALKER-SAMUEL[6], J. FAIRNEY[7], D. PENDSÉ[5,9], A. LATIFOLTOJAR[5,9], D. HAWKES[8], S. PUNWANI[5,9], and X. GOLAY[7]

[1]School of Psychology, [2]School of Optometry and Vision Science, [3]Centre for Brain Research, [4]Brain Research New Zealand, University of Auckland, Auckland, New Zealand

[5]Centre for Medical Imaging, [6]Centre for Advanced Biomedical Imaging, [7]Institute of Neurology, [8]Centre for Medical Image Computing, University College London, London, United Kingdom

[9]Department of Radiology, University College London Hospital, London, United Kingdom

GlucoCEST uses magnetic resonance imaging (MRI) to image glucose *in vivo* and has the potential to facilitate the metabolic assessment of cancers without exposure to ionising radiation. The aim of this study was to translate this new technique into the clinic and pilot it in a range of cancers including brain tumours. After implementing the technique on a 3T clinical MRI scanner and optimising the acquisition in vitro, we went on to trial glucoCEST in five patients (one with astrocytoma, two with lymphoma and two with squamous cell carcinoma). Patients fasted for eight hours and were then scanned prior to and sequentially following an oral glucose drink. As may be expected the astrocytoma demonstrated very little change in glucoCEST signal, but three out of the four of the other cases showed an increase in glucoCEST signal after oral ingestion of glucose. Our results indicate the clinical potential for glucoCEST MRI. Other endogenous CEST contrasts such as APT (Amide Proton Transfer) and NOE (Nuclear Overhauser Enhancement) that may have applications in neurological care, such as stroke imaging and glioma grading will also be discussed.

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